

# **Make the Pain Go Away**

## **Pediatric Pain Management: Update for Pharmacists**

### **Part II – Nonopioid and Adjuvant Analgesics**

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#### **Learning Objectives:**

1. Describe the common visceral, somatic and neuropathic pains present in the pediatric population.
2. List the common types of neuropathic pain affecting children and adolescents.
3. Identify patients with pain that is likely less sensitive to opioid analgesics.
4. List the nonopioid and adjuvant analgesics commonly used for pediatric patients.
5. Define the pharmacist's and technician's role in assessing and monitoring pediatric patients receiving nonopioid and adjuvant analgesics.
6. Develop an appropriate analgesic regimen for a child given specific patient factors.
7. Identify children at risk for adverse effects of nonopioid and/or adjuvant analgesics and recommend strategies for prevention.
8. Counsel patients, parents and caregivers on safe and effective use of nonopioid/adjuvant analgesics, including acetaminophen, nonsteroidal anti-inflammatory agents (NSAIDs), gabapentin, pregabalin, tricyclic antidepressants (TCAs), duloxetine and topiramate.

#### **Introduction and Background**

Failure to adequately treat or prevent pain during infancy or childhood may have detrimental effects on a child's development and result in enhanced pain responses later in life.<sup>1-2</sup> Adequate pain management throughout the continuum of life is an expectation in health care.<sup>3-6</sup> Pharmacists and pharmacy technicians have an integral role in pain management for the pediatric patient. The development of pharmacologic therapies has expanded options for providing safe and effective relief of pain and anxiety.<sup>6-9</sup>

The pharmacist can make important contributions to care of these children, including, but not limited to, selection and monitoring of pharmacologic therapies, adverse effect management and providing education to the patient/family and other members of the health care team.<sup>5,6</sup> Technicians can identify these children and their families and refer them to the pharmacist for additional counseling. Technicians can also ensure that the correct size dosage administration device is provided with oral liquids and become competent in compounding extemporaneous formulations.

The importance of assessing pain for infants and children was discussed in part I of this continuing education series on pediatric pain management.<sup>10</sup> Pain assessment can be challenging for infants and young children due to limitations in their ability to verbalize location, extent and intensity of pain. A review of pain assessment tools is included.

Data is accumulating on use of analgesics for prevention and treatment of pain in the pediatric population.<sup>7-10</sup> This second article in the series will focus on nonopioid and adjuvant analgesics. These include use of acetaminophen and nonsteroidal anti-inflammatory agents (NSAIDs) for musculoskeletal pain.<sup>4</sup> Syndromes with a neuropathic component, such as chronic regional pain syndrome (CRPS), radiculopathy, fibromyalgia and migraine, may respond poorly to opioids.<sup>11-14</sup> Tricyclic antidepressants (TCAs), serotonin reuptake inhibitors (SSRIs), serotonin/norepinephrine reuptake inhibitors (SNRIs, e.g., duloxetine) and anticonvulsants (gabapentin, pregabalin and topiramate) target multiple nerve mechanisms of pain.<sup>7-9</sup> Pharmacists

caring for children and adolescents must strive to become competent in the selection and monitoring of these pharmacologic therapies.

### Mechanisms and Clinical Characteristics of Pain

Mechanisms of pain may involve somatic (soft tissue and bone), visceral (abdominal organs), and neuropathic (nerve tissues).<sup>6</sup> An overview of pain mechanisms, common clinical presentation and effective medications for children and adolescents is included in Table 1. Identification of the mechanism of pain will assist clinicians in selection of the most effective pharmacologic interventions. It is important to remember that at any time the patient may also experience a combination of pain types. This situation indicates multiple medication therapy.

Pain lasting longer than six weeks and up to three months, or beyond the expected duration for healing, may be classified as chronic pain.<sup>5</sup> Referral to a multidisciplinary pediatric pain management program may be beneficial in these instances. Secondary to the multidimensional nature of pain affecting the psychological (mood, relationships, self-esteem), as well as physical aspects of the patient's life, it is often impossible for one clinician to address all of these aspects.

The presence of dedicated multidisciplinary pain management centers for children and adolescents is increasing across North America.<sup>15</sup> Many children with chronic pain conditions have a parent or family member with a pain history, such as migraine headache, lower back pain or shoulder/neck pain.<sup>16</sup> Implications to practice are to include parents and families in pain management interventions and education to assist children in coping. In addition, clinicians may be able to identify children at risk for chronic pain conditions. Children with chronic pain conditions may experience adverse physical, emotional and social consequences into adulthood as a result of fatigue sleep disorders and generalized pain.<sup>17</sup> They also tend to have greater symptoms of anxiety and depression.<sup>18</sup> This data indicates the need for treatment and early intervention, as well as continued follow up.

**Table 1. Overview of Pain Mechanisms and Medications for Children and Adolescents**

| <b>Pain Mechanism</b> | <b>Clinical Features</b>  | <b>Common Causes</b>   | <b>Medications</b>  |
|-----------------------|---|--|---|
| Somatic               | <i>Bones:</i> localized, dull or aching; movement worsens<br><i>Soft tissue:</i> localized, tender to touch   | Surgical procedures, lacerations, sprains, dislocations, fractures/trauma, tumor-bone metastases | Acetaminophen, corticosteroids, NSAIDs, opioids, topical and subcutaneous local anesthetics |
| Visceral              | <i>Abdomen:</i> deep, squeezing, poorly localized<br><br>Nausea/vomiting, bradycardia, hypotension ± sweating | Bowel ischemia, bowel obstruction, peritonitis, ovarian cysts, bladder distension, tumors        | Corticosteroids, intraspinal local anesthetics, NSAIDs, opioids                             |
| Neuropathic           | Burning, shooting, stabbing, shock-like;<br><i>Allodynia:</i> pain on light touch.                            | Fibromyalgia, Chronic Regional Pain Syndrome (CRPS), migraine, trigeminal neuralgia,             | <i>AEDs:</i> gabapentin and pregabalin<br><br><i>TCA:</i> amitriptyline and                 |

|  |  |  |   |
|--|--|--|---|
|  | <p>↑ or ↓ in pain perceptions; may occur at site distant from injury</p> | <p>herniated discs, diabetes, HIV, post-herpetic neuralgia, chemotherapy/radiation</p> | <p>Nortriptyline</p> <p><i>SSRIs</i>: fluoxetine treatment</p> <p><i>SNRIs</i>: venlafaxine and duloxetine;</p> <p><i>Opioids</i> (±): tramadol and methadone</p> <p>Ketamine</p> |
|--|--|--|---|

### Selected Chronic Pain Syndromes in Childhood and Adolescence: A Brief Overview

Children and adolescents often present with a variety of chronic pain syndromes that appear to be similar; however, they may differ in presentation or prevalence from the adult population.<sup>19</sup> Many of these syndromes are neuropathic in origin.<sup>19-21</sup> Neuropathic pain is caused by a lesion or dysfunction of the nervous system.<sup>20</sup> Pharmacological therapy that has been successful for pediatric patients combines nerve blocks and nonpharmacologic interventions, such as physical therapy and behavioral modification. A multidisciplinary program integrating these approaches is optimal.<sup>5,15</sup> Most of this data has been extrapolated from the adult population. Studies in the pediatric population are limited.

Pediatric patients with cancer may experience neuropathic pain from tumor infiltration or as a complication of treatment.<sup>21</sup> Children may also develop phantom limb pain after amputation.<sup>19,20</sup> Other types of neuropathic pain conditions that occur within the pediatric population are headache syndromes (migraine and tension), orofacial pain, trigeminal neuralgia, Bell's palsy occipital neuralgia and glossopharyngeal neuralgia.<sup>22-24</sup> Dental pain is more common than trigeminal neuralgia among children.<sup>25</sup> Many cases of orofacial pain in children may also be myofascial in origin.<sup>25</sup>

Fibromyalgia (FM) is a chronic central pain disorder characterized by multifocal pain and other symptoms, such as fatigue, insomnia, cognitive and memory impairment, and impaired functioning.<sup>11</sup> Juvenile primary fibromyalgia syndrome (JPFS) is characterized by chronic widespread musculoskeletal pain, multiple tender points, sleep difficulties, fatigue, headaches and irritable bowel symptoms.<sup>26</sup> Approximately one out of every six FM patients is under the age of 18 years old. Goals of therapy are to improve sleep (usually with a low-dose TCA) and pain management with NSAIDs.<sup>27</sup> Exercise and behavioral therapy to improve coping and decrease anxiety and depression are important components of treatment. Overall adherence with therapy by adolescents is poor.<sup>26,27</sup>

Complex regional pain syndrome (CRPS type I), formerly known as reflex sympathetic dystrophy, has been well documented in children as young as two years of age.<sup>19,20</sup> This condition usually develops after a minor trauma, such as bumps, sprains, fractures or surgery with a small or nonapparent nerve lesion at an extremity. The child develops painful symptoms out of proportion to the trauma.<sup>19</sup>

CRPS type II occurs after trauma with a large obvious nerve lesion.<sup>19,20</sup> Females are affected three times more frequently than males. The number of CRPS cases among adolescents and young adults is increasing. Therapy consists of TCAs, gabapentin, local anesthetic epidural injections and low-dose ketamine with cognitive behavioral therapy, physical therapy and transcutaneous electrical nerve stimulation (TENS).<sup>19</sup> Safety and efficacy studies in pediatric patients are lacking. Evidence is from experience and case reports, and extrapolated from adult data.<sup>19-21</sup>

Long-term outcomes of treatment of pain syndromes in pediatrics are limited by several factors, including difficulties in obtaining an adequately powered sample size for a study. These children have rare conditions and do not present with the same type of symptoms, severity or acuity. Therefore, it is difficult to design a study to produce valid results. The importance of collaborating with other centers must be explored to obtain increased study populations and overcome other barriers of pediatric analgesic research. We cannot continue to rely on using adult data for children and adolescents. The rapidly changing pharmacokinetics and pharmacodynamics of the child during growth, as well as the plasticity of the developing neuronal tissue, must be considered when determining analgesic dosage regimens.<sup>29,30</sup> The pharmacist should continue to review new data in the literature as this area of practice is rapidly evolving.

### **Role of Nonopioid Analgesics**

Opioids may be used successfully for managing chronic noncancer pain with careful review of risk factors for abuse/diversion and supervision of use. However, their use for neuropathic pain remains controversial and weak evidence supports significant pain relief with long-term oral therapy.<sup>12-14</sup> Many parents/children discontinue opioid use secondary to adverse effects or lack of effects.<sup>5,21</sup> Studies are short-term and from the adult population.<sup>12-14</sup>

Nonopioid analgesics (NSAIDs) and acetaminophen are the first step on the World Health Organization (WHO) ladder for management of mild or moderate cancer pain.<sup>31</sup> These agents should be considered for initial analgesia for mild to moderate pain. Ketorolac, a NSAID available for IV administration, is effective for moderate to severe pain.<sup>6,32</sup> Acetaminophen and NSAIDs are effective for somatic (soft tissue and bone) pain and NSAIDs have been used for visceral pain.<sup>6,21</sup> Overall neuropathic pain is relatively opioid insensitive or may be partially opioid sensitive.<sup>13,21</sup> Selected patients with fibromyalgia and CRPS may respond to NSAIDs.<sup>19,26</sup>

Acetaminophen and NSAIDs have opioid-sparing effects and are available as opioid combination products (e.g., codeine, hydrocodone).<sup>32,33</sup> These agents used with opioids may decrease opioid side effects, including constipation, nausea, vomiting and sedation.<sup>6</sup> Consider the nonopioids whenever a child has a contraindication to opioids or presents with a pain condition that may be partially opioid or completely insensitive.<sup>6</sup>

### **Acetaminophen**

Since reports emerged during the 1970s on the association between aspirin and Reye's hepatic encephalopathy in children, acetaminophen became the most commonly used analgesic for mild pain in pediatric patients.<sup>34</sup> Acetaminophen has a well-known safety and efficacy profile in children.<sup>34-40</sup> Analgesia is via potent inhibition of prostaglandin synthesis within the central nervous system (CNS), in addition to blockade of generation of nociceptive impulses.<sup>36,37</sup> Acetaminophen antagonizes N-methyl-D-aspartate (NMDA) and substance P in the spinal cord, yet lacks anti-inflammatory properties. The recommended oral dose of acetaminophen is 10 to 15 mg/kg every 4-6 hours (limit 75 mg/kg/day for children, or 4,000 mg daily for adults).<sup>33</sup>

Rectal administration of acetaminophen produces delayed and erratic absorption.<sup>36-38</sup> Avoid the rectal route of administration unless specifically discussed with the parent/caregiver, as it may result in suprathreshold dosing.<sup>38</sup> The usual single rectal dose for acetaminophen of 35-45 mg/kg should produce adequate serum concentrations for analgesia. Rectal administration prolongs clearance of acetaminophen; therefore, increase the dosing interval to every 6-8 hours.<sup>38</sup> If additional rectal doses of acetaminophen are needed, limit subsequent doses to a maximum of 20 mg/kg/dose to minimize accumulation.<sup>36-38</sup>

Hepatic toxicity has occurred with excessive dosing and/or chronic use of acetaminophen in children.<sup>41</sup> Caregivers must be informed of risks of excessive dosing of this ubiquitous analgesic

available in numerous formulations.<sup>42</sup> Technicians can direct patients/caregivers to the pharmacist for reviews of medication profiles to screen for multiple sources of acetaminophen prior to purchasing over-the-counter (OTC) products. Concomitant administration of acetaminophen from OTC and prescription products can result in excessive dosing and hepatotoxicity.<sup>41,42</sup> Pharmacists must inquire about all products that the child is taking to avoid potential toxicity.

### Nonsteroidal Anti-inflammatory Agents (NSAIDs)

NSAIDs are useful in treating acute pain from various causes, including trauma, surgery and inflammation.<sup>43</sup> Postoperatively, IV ketorolac can improve analgesia for a child without contributing to opioid adverse effects.<sup>32,44</sup> NSAIDs inhibit cyclooxygenase (COX) 1 and 2, blocking prostaglandin and thromboxane synthesis both centrally and peripherally.<sup>43</sup> The benefit of selecting COX-2 is a lower risk of gastrointestinal and hematologic adverse effects.

Adverse effects have been also been reported with this class of NSAIDs agents in children.<sup>43</sup> Secondary to potential cardiovascular toxicity, paucity of pediatric data and higher cost, the selective COX-2 NSAIDs (e.g., celecoxib) are not recommended for routine analgesia.<sup>43-46</sup> Celecoxib is primarily prescribed by pain management specialists, pediatric rheumatologists or orthopedic surgeons.<sup>46,47</sup> Currently, eight nonselective NSAIDs (etodolac, ibuprofen, indomethacin, ketorolac, meloxicam, naproxen, oxaprozin and tolmetin) and one selective COX-2 NSAID (celecoxib) are Food and Drug Administration (FDA)-approved pediatric indications.<sup>46</sup> Others (e.g., sulindac) are used off-label.<sup>48</sup> NSAIDs commonly used to treat pain in children and adolescents are reviewed in Table 2.

**Table 2. NSAIDs Commonly Used as Analgesics for Children and Adolescents**

| Nonselective Cyclooxygenase (COX)-1 and -2 Inhibitors |  |  |
|---|--|--|
| NSAID   | Dose/Frequency/Route   | Considerations   |
| Ibuprofen   | 4-10 mg/kg/dose, every 6-8 hours, oral or IV   | <ul style="list-style-type: none"> <li>Oral liquid: 20 mg/mL; tablets: 200, 400, 600 &amp; 800 mg. Limit: 3.2 g/day adult</li> <li>IV injection: 100 mg/mL Caldolor®</li> <li>Many OTC formulations</li> <li>Not recommended for children under three months of age</li> </ul> |
| Ketorolac   | 0.5 mg/kg/dose, every six hours, IV (oral not used for pediatrics)                   | <ul style="list-style-type: none"> <li>Max dose for patients under 50 kg = 15 mg; more than 50 kg = 30 mg</li> <li>Avoid use for longer than five days</li> <li>Loading dose no longer recommended</li> <li>Off-label use for those under two years of age</li> </ul>          |
| Naproxen  | 5-7 mg/kg/dose, every 8-12 hours, oral<br>Juvenile rheumatoid arthritis (JRA): 10-15 | <ul style="list-style-type: none"> <li>Oral liquid/tablets</li> <li>OTC formulations not approved for those under 12 years of age</li> <li>Avoid sun exposure in children with JRA taking naproxen (12 percent</li> </ul>  |

|  |   |  |
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|  | mg/kg/day divided in two doses (max dose: 1 g/day)<br><br><i>Adult:</i> 250-500 mg, limit 1,250 mg/day  | have blistering skin reaction-pseudoporphyria)   |
| Sulindac   | 2-4 mg/kg/day divided in two doses, oral (max dose: 6 mg/kg/day), limit 400 mg/day)<br><br><i>Adult:</i> 150-200 mg twice daily (max dose: 400 mg/day)          | <ul style="list-style-type: none"> <li>• Tablets: 150, 200 mg</li> <li>• Alternate NSAID with twice daily dosing to improve adherence with school schedule or lack of response to first-line NSAIDs</li> <li>• Michigan Medicaid formulary NSAID</li> </ul>  |
| <b>Selective Cyclooxygenase (COX)-2 Inhibitors</b> |   |  |
| <b>NSAID</b>                                       | <b>Dose/Frequency/Route</b>   | <b>Considerations</b>  |
| Celecoxib  | <p>≥ 2 yrs: JRA<br/>         ≥ 10 kg to ≤25 kg: 50 mg twice daily oral<br/>         &gt; 25 kg: 100 mg twice daily<br/>         Off-label use for analgesia</p> | <ul style="list-style-type: none"> <li>• Capsule: 50, 100, 200, 400 mg (generic)</li> <li>• Consider when patient lacks response to nonselective NSAIDs</li> <li>• Michigan Medicaid Carve-Out drug benefit</li> <li>• MICHild – HMO requires pre-approval/demonstration of failure or side effects with first-line agents</li> <li>• Possible ↓ GI/renal side effects vs. nonselective NSAIDs; continue to monitor, serious side effects (e.g., disseminated intravascular coagulation in children with JRA)</li> <li>• Use with caution in CYP2C9 poor metabolizers</li> </ul> |

### Celecoxib

Celecoxib, a selective COX-2 inhibitor continues to be used for adults and children with rheumatoid arthritis.<sup>43</sup> Celecoxib has been effective for children with cancer pain and chronic pain syndromes (e.g., fibromyalgia, CRPS) or those failing to respond to first-line nonselective NSAIDs.<sup>43</sup> Children with sulfonamide hypersensitivity may cross-react to celecoxib, underscoring the importance of a thorough allergy history.<sup>47</sup>

### Ibuprofen

Ibuprofen, a nonselective inhibitor of COX-1 and -2 isoforms is the most commonly prescribed NSAID for pediatric patients.<sup>43,46</sup> A single dose of ibuprofen provided better analgesia than acetaminophen or codeine in children with acute musculoskeletal pain from minor injury in a prospective double blind randomized placebo controlled trial.<sup>35</sup> There were several limitations to the

study, including only 52 percent of subjects reported adequate analgesia 60 minutes after dosing. The investigators concluded that ibuprofen alone might not provide sufficient pain relief in musculoskeletal trauma. There was no difference in frequency of adverse effects among the three study analgesics. The types of injuries sustained by children in the study might have warranted more aggressive analgesic management, including repetitive dosing, or stronger opioid or combination therapy.

Ibuprofen was demonstrated to be more effective than acetaminophen for pain from tonsillitis and migraine.<sup>39,40</sup> The usual oral dose of ibuprofen is 4-10 mg/kg every 6-8 hours, with a maximum daily dose of 40 mg/kg (not to exceed 3.2 g/day in adults). Ibuprofen is available in several oral liquid and tablet strengths without a prescription.<sup>33</sup> Routine analgesic use is not recommended in ages under three months secondary to limited data. High potential exists for dosage errors and product confusion. As with acetaminophen, clinicians must provide parents and caregivers with clear instructions.

### **Ketorolac**

Ketorolac is a parenteral NSAID approved for analgesia in patients older than two years of age.<sup>44</sup> It has been used for children less than two years of age, despite sparse data regarding safety in this age group.<sup>49</sup> Secondary to established analgesic and opioid sparing effects, ketorolac is used as an adjunct to patient controlled analgesic (PCA) during the post-operative period.<sup>32</sup> Ketorolac therapy should not exceed five days secondary to limited data regarding extended use.<sup>47</sup> Possible adverse effects in children include nephrotoxicity, bronchospasm and increased post-operative bleeding.<sup>44</sup> There is limited experience with oral ketorolac in children; however, IV ketorolac has been administered to patients as young as one month without apparent adverse effects with data from small, retrospective trials.<sup>44,49</sup> These results are confined to hospitalized children with monitored fluid status. During ketorolac therapy, close monitoring of fluid status, renal function and careful assessment for evidence of bleeding is imperative.

### **NSAIDs for Orthopedic Patients – A Controversial Issue**

Administration of NSAIDs to orthopedic patients during the immediate post-operative period is controversial because of possible inhibitory effects on osteogenesis and bone healing.<sup>50,51</sup> Orthopedic surgeons and other clinicians may be hesitant to prescribe NSAIDs during the first 24-72 hours post-op for children undergoing spinal fusion or extensive fracture repair and/or instrumentation secondary to fears of delayed healing or nonunion of fracture by the prostaglandin inhibitory effects of these medications.<sup>32</sup> Data is extrapolated primarily from animal studies, exposure to high/toxic doses of NSAIDs and small case series. Confirmation in well-powered, controlled prospective trials is needed. Pharmacists must communicate with local orthopedic surgeons to develop NSAID analgesic protocols to improve patient care and build team relationships.

### **Adverse Effects of NSAIDs**

Frequent adverse effects associated with NSAID use are nausea, dizziness and headache.<sup>43</sup> Gastric and renal side effects associated with therapeutic NSAID use are less prevalent in children when compared with adults.<sup>46,52,53</sup> This is in spite of up to 15 percent of parents reporting discontinuing OTC ibuprofen use during treatment for fever due to their child's gastrointestinal complaints.<sup>53</sup>

Several NSAIDs (diclofenac, ibuprofen, naproxen and celecoxib) are metabolized by hepatic cytochrome P450 2C9 (CYP2C9).<sup>53</sup> Inherited genetic polymorphisms in CYP2C9 coding sequence results in decreased enzyme activity in approximately 6-10 percent of Caucasians.<sup>53</sup> Polymorphisms

of CYP2C9 may increase the risk of gastric bleeding and NSAID-related gastroduodenal bleeding.<sup>54</sup> Further studies are needed to validate the clinical effectiveness of using genotyping for preventing adverse drug reactions with NSAID therapy, especially in children.

Nephrotoxicity may be present in 1-5 percent of patients with regular NSAID use, regardless of COX-1 and COX-2 selectivity by patients of all ages.<sup>45,52,55</sup> NSAIDs contribute to the 16 percent incidence of acute kidney injury (AKI) in older children and adolescents admitted to the pediatric intensive care unit.<sup>52,55</sup> Risk factors for NSAID-induced AKI include dehydration, impaired sodium and water excretion, use of concomitant nephrotoxic medications and pre-existing renal impairment.<sup>55</sup>

### **General NSAID Precautions**

General precautions for NSAIDs include asthma or aspirin sensitivity, as these patients may have an aspirin-evoked bronchospasm, which exhibits cross sensitivity to NSAIDs.<sup>43,46</sup> Hepatic function should be evaluated prior to NSAID therapy.<sup>43</sup> Liver function tests (LFTs) should be obtained regularly during prolonged treatment to monitor for liver injury and failure.<sup>43</sup>

Diclofenac (oral and topical formulations) has been shown to increase LFTs and cause serious hepatotoxicity. A genetic predisposition, possibly in combination with environmental factors, has been hypothesized.<sup>56</sup> Diclofenac has been used in treating JRA; however, it should be avoided for pediatrics use unless a clear benefit can be demonstrated.<sup>57</sup>

Patients with bleeding disorders (e.g., low platelets) and those receiving anticoagulants should be carefully evaluated for bleeding risk versus benefit prior to initiating NSAID therapy.<sup>43,46,57</sup> Renal dysfunction, dehydration and gastrointestinal bleeding or ulcers increase risk of NSAID-induced adverse effects.<sup>55</sup> Water and sodium retention from NSAIDs may exacerbate or cause hypertension or CHF. All NSAIDs have the U.S. boxed warning of associated increased risk of adverse cardiovascular thrombotic events, potentially fatal myocardial infarction and stroke.<sup>43</sup> Adverse cardiovascular events associated with NSAID use in the pediatric population cannot be differentiated from the patients underlying cardiac comorbidities.<sup>57</sup>

Use of more than one NSAID at a time is not recommended.<sup>43-45</sup> Pharmacists are responsible for monitoring the numerous NSAID medication-medication and medication-disease interactions.<sup>43</sup> Safe and effective therapy for this vulnerable population requires pharmacist and technician participation.

### **Antidepressants as Analgesics in Pediatric Practice**

Antidepressant medications used as analgesics for children and adolescents include the tricyclics (e.g., amitriptyline, nortriptyline), selective serotonin and serotonin/norepinephrine reuptake inhibitors (e.g., fluoxetine, citalopram, duloxetine).<sup>58-61</sup>

The pharmacology of these medications interacts with pain pathways via norepinephrine and serotonin reuptake inhibition, direct and indirect opioid receptors interaction; antagonism of histamine, cholinergic and NMDA receptors; inhibition of neuronal channel ion activity; and adenosine reuptake.<sup>2,7,19-21,28</sup> TCAs have the most data with respect to pain management in children, yet they are not FDA-approved for this indication.<sup>59</sup> The SSRIs are better tolerated in comparison to TCAs because of less anticholinergic side effects. There is less data for managing pain in children with these agents than when compared with adults.<sup>60-63</sup> Fluoxetine, escitalopram, fluvoxamine and sertraline are approved for use in children older than eight years of age with depression and/or obsessive compulsive disorder. Trazadone, a highly-sedating SSRI/agonist activity antidepressant, has minimal effects on pain and is best avoided due to side effects of hypotension and drowsiness.<sup>21,62</sup> All antidepressant use for analgesia in pediatrics is off-label, although data exists in

the literature supporting dose ranges and effectiveness.<sup>58,60,65</sup> A review of frequently prescribed antidepressants for analgesia for pediatric patients is in Table 3.

**Table 3. Frequently Prescribed Antidepressants for Analgesia: Pediatric Patients**

| <b>Tricyclic Antidepressants (TCAs)</b>                     |  |  |
|---|--|--|
| <b>TCA</b>  | <b>Dose/Frequency</b>  | <b>Considerations</b>  |
| Amitriptyline   | <p><b>Chronic pain:</b> 0.1 mg/kg oral at bedtime; ↑ weekly or as tolerated to 0.5-2 mg/kg at bedtime; variable: dose for pain &lt; depression; max dose = 100 mg</p> <p><b>Migraine prophylaxis:</b> 0.25-1.7 mg/kg/day</p> | <ul style="list-style-type: none"> <li>• Avoid serotonin-like medications, ETOH, St John's Wort; ↑ warfarin concentrations</li> <li>• Common side effects: dry mouth, constipation, orthostatic hypotension and urinary retention</li> <li>• Counsel with medication guide on suicidal thinking; may unmask mania in bipolar patients; review for family history of syncope, sudden death (risk of prolonged QTc); consider ECG screening; ↓ seizure threshold</li> <li>• May need pre-approval: Michigan Medicaid HMOs</li> <li>• Photosensitivity precautions: SPF ≥ 15</li> <li>• Weight gain precautions: advise taking dose two hours prior to bedtime for sleep</li> </ul> |
| Nortriptyline   | <p><b>Adolescents-chronic pain:</b> start at 10 mg oral at bedtime daily; ↑ after seven days to 25 mg daily if tolerated; then ↑ weekly by 25 mg to max of 100 mg/day; variable: dose for pain &lt; depression</p>           | <ul style="list-style-type: none"> <li>• Available as 10 mg/mL solution</li> <li>• Caution patient/parents to avoid abrupt discontinuation of this and all antidepressants to avoid withdrawal syndrome-tachycardia, flushing, tremor, NV and irritability.</li> <li>• Consider ECG screening at baseline</li> <li>• Less sedation, anticholinergic effects vs. amitriptyline; (metabolite), ↑ arrhythmia risk vs. amitriptyline</li> <li>• Monitor for addition of medications that also prolong QTc (e.g., methadone)</li> <li>• Monitor adherence closely</li> <li>• Provide only limited amounts of TCA to avoid intentional overdose</li> </ul>                             |
| <b>Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)</b> |  |  |
| <b>SNRI</b>   | <b>Dose/Frequency</b>  | <b>Considerations</b>  |
| Duloxetine  | >10 yrs: start 30 mg oral daily; ↑ to 60 mg daily if needed; 30, 60 mg tablets   | <ul style="list-style-type: none"> <li>• Administer dose in morning; may cause hyperactivity, unmasking of mania</li> <li>• Approved for fibromyalgia pain in adults</li> <li>• Common side effects: nausea, dry mouth and dizziness, ± drowsiness</li> <li>• Requires pre-approval: Michigan Medicaid HMOs</li> </ul>   |

### **When to Recommend an Antidepressant as Analgesia for a Pediatric Patient**

TCA's are indicated for burning-type pain.<sup>31</sup> TCA's have been used in pediatric patients with chronic cancer pain syndromes, migraine headache, abdominal migraine, chronic pelvic pain, phantom limb pain, chronic regional pain syndrome (CRPS) and fibromyalgia.<sup>19-21,59,62-64</sup> These agents have been used to treat a variety of types of neuropathic pain syndromes in children, including pain after spinal cord injury and traumatic neuropathic pain.<sup>19-21</sup> Chronic pain can disrupt sleep, becoming worse at night.<sup>5</sup> The sedating properties of TCA's may be helpful for improving sleep when the dose is administered two hours prior to bedtime.<sup>62-63</sup>

Duloxetine and milnacipracin are SNRIs with approved indications for treatment of fibromyalgia in adults.<sup>26,27</sup> Data is available on use of duloxetine in older children and adolescents in the form of case reports.<sup>7,60,61</sup> Experience with milnacipracin in pediatrics is very limited and this agent is not used in routine practice.<sup>27</sup> Adult data has shown that highly-selective SSRIs (e.g., citalopram) do not produce significant analgesia in FM.<sup>27,59</sup> SSRIs with more effect on norepinephrine and less on serotonin (e.g., fluoxetine or sertraline) may be more effective in treating FM, although at higher doses.<sup>11,27,59</sup> The SNRIs have a better side effect profile than the TCA's and have been more effective in the treatment of FM.<sup>26,27,62-64</sup> The SNRIs may be stimulating and should be administered in the morning to avoid interfering with sleep.<sup>59</sup>

### **Patient Monitoring Points**

Chronic pain may result in mood disorders or depression.<sup>5,17,18</sup> A beneficial effect of using antidepressants for analgesia may be improved mood, yet do not replace psychological counseling or support. All antidepressants are labeled with the warning about the increased risk of suicidal thinking and behavior in children and adolescents undergoing treatment with antidepressants.<sup>65</sup>

Pharmacists must counsel about this risk with every new and refill prescription for these medications. Technicians can assist in ensuring that FDA medication guides are dispensed with every antidepressant prescription. Prescriptions should be written for the smallest quantity possible and adherence carefully monitored by the parent/caregiver. Changes in a patient's mood or affect should be assessed and communicated to the prescriber immediately. In addition, many medications and supplements, such as St. John's Wort or additives in energy drinks, may interact with antidepressants.<sup>62,63</sup> Children and adolescents must be educated not to use these without informing their physician/pharmacist.

### **Antiepileptic Drugs (AEDs) for Neuropathic Pain Management in Children**

Children with neuropathic pain syndromes may describe their pain as an intermittent "off and on" stabbing sensation.<sup>19-21,27,28</sup> The abrupt onset and temporal nature of neuropathic pain attacks can mimic seizure activity at the neuronal level.<sup>19-21</sup> Antiepileptic drugs (AEDs) are first- or second-line therapy, as they depress neuronal hyperexcitability.<sup>66-70</sup> Historically, anticonvulsant medications used for pain in children include carbamazepine, phenytoin, valproic acid and clonazepam.<sup>66-67</sup> Many of these AEDs interact with other drugs, and/or have unacceptable adverse effects (e.g., extreme drowsiness, weight gain, cognitive impairment) without significant analgesia in children.<sup>66</sup> Newer AEDs, such as gabapentanoids and topiramate, are commonly prescribed (see Table 4).<sup>67-69</sup>

**Table 4. Selected Antiepileptic Drugs (AEDs) for Neuropathic Pain for Children**

| AED        | Dose/Frequency  | Considerations   |
|------------|---|--|
| Gabapentin | <p><b>Neuropathic pain:</b><br/> <i>Child</i><br/>                     Start 5 mg/kg/dose at bedtime; increase to 5 mg/kg/dose twice daily increase to three times daily on day three (if tolerated); titrate to effect (range 8-35 mg/kg/day)</p> <p><i>Adult/ adolescent</i><br/>                     100 mg 3 times/day; titrate to effect at weekly intervals to 900 mg/day (1,800-2,400 mg/day); no benefit at &gt; 3,600 mg</p> | <ul style="list-style-type: none"> <li>• Adjust dose in renal dysfunction- clearance proportional to CrCl</li> <li>• Common side effects: nausea, vomiting, constipation, tremor, dizziness</li> <li>• Counsel: pregnancy category C</li> <li>• Ketorolac may ↓ serum gabapentin conc.</li> <li>• Suicidal consult/ provide medication guide</li> <li>• Available as tablets, capsules and oral solution</li> <li>• Weight gain, peripheral edema (10 percent) may be bothersome; behavioral problems (aggression/hostility/irritability)</li> </ul> |
| Pregabalin | <p><b>Neuropathic pain:</b><br/> <i>Child &gt;12 yrs</i><br/>                     50-75 mg at bedtime, then 75 mg twice daily; titrate to 225 mg (if tolerated)</p> <p>Initiate regimens at bedtime on weekend to avoid interference with school</p> <p>25, 50, 75, 100, 200, 300 mg capsules</p>   | <ul style="list-style-type: none"> <li>• Adjust dose in renal dysfunction; antidepressant effect</li> <li>• Common side effects: peripheral edema, sedation, dizziness, dry mouth</li> <li>• Consider for patients with inadequate response or adverse effects with gabapentin</li> <li>• Counsel: pregnancy category C</li> <li>• FDA approved for fibromyalgia in adults</li> <li>• May require pre-approval: Michigan Medicaid HMOs</li> <li>• Suicidal consult/ provide medication guide</li> </ul>  |
| Topiramate | <p><b>Migraine prophylaxis:</b><br/> <i>Adult/ adolescent</i><br/>                     Initiate: 25 mg/day; increase to twice daily, increasing weekly to maximum of 100 mg twice daily (as tolerated); adult dose maximum= 200 mg twice daily</p> <p><i>Children (2-15 yrs)</i><br/>                     2-3 mg/kg/day</p> <p><i>Children ≥ 2 yrs</i></p>  | <ul style="list-style-type: none"> <li>• Common AE teen: fatigue/sedation</li> <li>• Counsel: pregnancy category C, cleft palate</li> <li>• Decrease appetite and monitor weight</li> <li>• May decrease serum bicarbonate and levels of oral contraceptives</li> <li>• Monitor for: metabolic acidosis, decreased sweating, dehydration, renal stones, visual changes (ocular syndrome-myopia/glaucoma)</li> </ul>  |

|  |                               |   |
|--|-------------------------------|---|
|  | Seizure dose is 5-9 mg/kg/day | <ul style="list-style-type: none"> <li>• Suicidal consult/provide medication guide</li> <li>• Valproate may predispose to hyperammonemia</li> </ul> |
|--|-------------------------------|---|

### Gabapentin and Pregabalin

The neuronal calcium channels at pre-synaptic spinal terminals of primary afferent nociceptors release excitatory amino acids when activated. Abnormal activation of these neurons causes central sensitization.<sup>19-21</sup> The gabapentanoids, gabapentin and pregabalin bind to the  $\alpha 2\delta$ -subunit of calcium channels modulating neuronal excitability.<sup>20</sup> These agents have a better side effect profile, minimal medication interactions and are easily titrated compared with good response for neuropathic pain syndromes.<sup>11,66</sup> Pregabalin is similar to gabapentin in that it is a structural, not a functional, analogue of the neurotransmitter GABA.<sup>66</sup> Pregabalin is also the first AED with controlled substance status secondary to side effects of euphoria and somnolence.<sup>66</sup> Advantages over gabapentin are twice daily dosing and possibility of an antidepressant effect.<sup>11,67</sup> Patients experiencing headache or adverse effects with gabapentin may be able to tolerate pregabalin.<sup>11</sup> Data are accumulating on the use of these agents in pediatric patients for neuropathic pain syndromes.<sup>67</sup>

### Topiramate

Topiramate has several mechanisms of anticonvulsant action, including blockade of neuronal sodium channels and enhancement of GABA inhibition.<sup>66</sup> These actions give topiramate its effectiveness in migraine prophylaxis.<sup>68,69</sup> Pediatric migraine can be disabling, resulting in a loss of productivity and decreased quality of life.<sup>11</sup> Prophylactic therapy can decrease frequency of headache and accompanying disability, allowing the child or adolescent to participate in school, sports or social activities.<sup>68,69</sup> Topiramate is also approved for this indication in adults.<sup>66</sup>

There is pediatric efficacy and safety data available on topiramate from use in pediatric seizures.<sup>66</sup> Adverse effects that are of particular concern in the pediatric population are weight loss associated with a decrease in appetite, somnolence and an increased risk of nephrolithiasis.<sup>66</sup> Over-use of calcium supplements can also increase the risk of nephrolithiasis and metabolic acidosis.<sup>66</sup> Maintenance of fluid intake and acid base balance are recommended for children receiving topiramate.<sup>66</sup> Young children in warm weather are at the highest risk. Pharmacists and technicians have an important role in educating parents/caregivers on proper hydration.

### Topical Anesthetic Patches-lidocaine 5% Patch

Lidocaine 5% patch, an adhesive containing 5 percent lidocaine, has been shown to be effective in neuropathic and nonneuropathic pain from osteoarthritis, lower back pain, post-herpetic neuralgia and painful diabetic neuropathy.<sup>9,71,72</sup> Current data on use in children is limited.<sup>9</sup> Lidocaine is a peripheral acting topical anesthetic, which reduces ectopic neural discharge from damaged peripheral sensory nerves via sodium channel blockade.<sup>73</sup> The patch produces analgesia on tissues without skin numbness and loss of sensation to temperature or touch.<sup>71-73</sup>

Lidocaine has a narrow therapeutic index (2-5 mcg/mL).<sup>72,73</sup> Symptoms of CNS toxicity, including anxiety, psychosis, tremor and paresthesias, occur as early signs of systemic absorption. Arrhythmias usually occur at 6 mcg/mL. Mean serum lidocaine concentrations were measured to be 1.3 mcg/mL in adult volunteers after 11 hours of application.<sup>72</sup> Adults have applied up to four patches without adverse effects, yet only one patch per application is prudent for children and adolescents until further data is available.<sup>9,71-73</sup> Approximately 3 percent of the medication is absorbed with intact skin on healthy volunteers.<sup>71</sup> The patch should not be applied to broken or

inflamed skin. Application time should not exceed 12 hours. A child may be predisposed to percutaneous absorption of medication when compared with adults. Localized types of neuropathic pain (e.g., neuropathic scar pain, post-herpetic neuralgia) appear to respond best.<sup>19</sup>

Patches may be cut to fit the area of application prior to removal of liner.<sup>73</sup> Pharmacists must caution patients to remove the patch after 12 hours of application and to not expose the patch to heat (e.g., hot packs, heating pads). Tanning booths remain popular in Michigan among adolescents and the pharmacokinetics of transdermal medications from a patch system may be affected by exposure to ultraviolet light.<sup>73</sup> Patch medications are often overlooked during a medication history. Remember to ask your patients directly about the use of patches. Michigan Medicaid or health maintenance organizations (HMOs) for children may not provide medical benefit for lidocaine 5% patch product, which can be expensive (\$244 USD for 30 patches, according to the 2011 Average Wholesale Price Red Book™).

## Key Points for the Pharmacist and Technician

- When selecting an analgesic for a child, consider type and severity of pain, concomitant disease states and medication interactions, as well as the clinician's familiarity with the analgesic and type of insurance.
- Overall, neuropathic pain responds less well to opioids than non-neuropathic pain; however, physicians should not withhold opioid therapy in children with CRPS, fibromyalgia, migraine or other conditions, if appropriate.
- Data is accumulating on the dosing and long-term effects of these medications in children. We need to review the literature and communicate with specialists in this area to stay current.
- Remember to conduct a thorough medication and allergy history
- Screen for medication interactions
- Calculate weight-based and age appropriate doses
- Provide appropriate oral medication administration devices (dosing cups, oral syringes)
- Remember to provide counseling, and keep in mind the pregnancy risks of medications and mood changes with AEDs and antidepressants; provide medication guides where required
- Monitor adherence and recommend strategies for improvements
- Review for medication-medication and medication-disease interactions
- Many analgesics have teratogenic effects; inform patient/caregiver of risks and counsel appropriately
- Monitor OTC selection by child/parent/caregiver; make recommendations to avoid interaction/duplication
- Make recommendations consistent with the child's third party constraints; assist in pre-approvals for medication benefits (e.g., formulary issues, medication therapy selections)
- Communicate with pain management team
- Provide education to children and families on pain management

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*Care has been taken to confirm the accuracy of the information presented and to confirm all doses. However, as pharmacotherapy is a constantly changing practice, the author and MPA are not responsible for errors or omissions, or for any consequences from application of the information in this article and make no warranty, expressed or implied, with respect to the currency, completeness or accuracy or the contents of the publication. Application of this information in a particular clinical situation remains the professional responsibility of the clinician. Pharmacy practice is a process of life-long learning and practice changes occur over time. The author has exerted every effort to ensure that drug selection and dosage set forth in this article are in accordance with current recommendations and practice at the time of publication. In view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert of each drug for any change in dosage, indication, added warnings, and precautions. Many of the drugs discussed in this article are used as Food and Drug Administration (FDA) "off-label" indications for pediatric analgesia. The clinician must be aware of all monitoring and assessment parameters regarding their safe clinical use prior to initiation.*

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## Posttest Questions

1. Tamika, a 10-year-old girl, presents to the pain management clinic with burning and tingling pain in her left foot. The skin on her foot turns dark blue at times and feels numb to the touch. These symptoms started about three weeks after she sprained her ankle during a softball game last summer. She says her pain is 8/10 and that the Norco 5/325 that her pediatrician gives her does not help. Her pain syndrome is most likely:
  - a. Bone fracture
  - b. Osteoarthritis
  - c. Fibromyalgia
  - d. Complex Regional Pain Syndrome (CRPS)
2. A high number of children with chronic pain have a family pain history (e.g., parent with a chronic pain condition), which affects the child's ability to cope with their condition. Therefore, family members must be included in pain management education and counseling.
  - a. True
  - b. False
3. Matt, a 15-year-old male adolescent, had a lung biopsy under anesthesia with analgesia via a thoracic epidural catheter. There were no complications during biopsy. The catheter was removed on post-op day one, and patient was discharged and went home. His pain increased at the scar site after removal of the catheter. Over the next month, the pain became worse. Matt rates the pain as 7 to 9/10 and describes it as a "shooting" sensation in his chest. Appropriate doses of ibuprofen, hydrocodone and acetaminophen do not help. The best option for management is:
  - a. Celecoxib
  - b. Morphine
  - c. Lidocaine 5% patch
  - d. Fentanyl transdermal system, 12.5 mcg/hr
4. The therapeutic class of medications that may interfere with bone healing after fracture and orthopedic surgical procedures is:
  - a. Opioids
  - b. Nonsteroidal anti-inflammatory agents
  - c. Tricyclic antidepressants
  - d. Acetaminophen
5. Maya, a 10-year-old girl with chronic migraine headache, has amitriptyline 10 mg daily prescribed by her pediatrician. The most appropriate time of day for Maya to take amitriptyline is:
  - a. With breakfast daily before school
  - b. Two hours before bedtime daily to optimize its sedating effects and avoid morning drowsiness
  - c. In the afternoon, after school, in order to avoid side effects
  - d. The time of day does not matter with this medication.

6. Joey, a 7-year-old boy, fell from the slide at the local playground onto his side. He presents with a large hematoma forming on his left hip and leg. Radiographs are negative for fracture. He describes his pain as “someone hitting him in the leg.” The mechanism of pain is most likely:
- Neuropathic; recommend gabapentin titration according to weight
  - Visceral; recommend hydrocodone and acetaminophen according to weight
  - Somatic; recommend ibuprofen 4-10 mg/kg every 6-8 hours
  - None of the above
7. Terrell is a 12-year-old male child with chronic migraine-type headache s/p head injury sustained in a school bus accident in preschool. His BMI is 35 percent and he has a family history of type II diabetes. Terrell wants to taper off the hydrocodone and acetaminophen that he currently uses to control his headache episodes because “they no longer help.” An appropriate choice for a preventative agent for Terrell is:
- Topiramate
  - Amitriptyline
  - Gabapentin
  - Nortriptyline
8. Pain of neuropathic origin may be insensitive or partially sensitive to opioid analgesics.
- True
  - False
9. Tasha, a 12-year-old girl, has persistent muscle pain from a complex spinal fusion eight weeks ago for idiopathic scoliosis. The orthopedic surgeon has cleared her for return to school. Her school has a strict “no medication” policy, and her mother is unable to come to administer a mid-day dose of ibuprofen for pain. She is insured by MIChild Medicaid. The surgeon wrote for Celecoxib for the BID dosing schedule. An alternative NSAID for this child would be:
- to increase the ibuprofen dosing interval to BID.
  - diclofenac.
  - ketorolac oral tablets.
  - sulindac tablets (weight-based dosing twice daily).
10. Amy, a 16-year-old female adolescent, is considering taking duloxetine 30 mg daily in morning and celecoxib 100 mg daily for fibromyalgia pain. She is currently taking ibuprofen OTC, as needed, for menstrual cramps. She denies ETOH use, smoking, medication abuse and is not sexually active. Amy lives at home with her parents and is active in her group at church. She is allergic to sulfa and has an allergic reaction of rash/hives to Bactrim 2010. Based on this information, what recommendation(s) should be given to the patient?
- Celecoxib may cause a reaction in a sulfa allergic patient (sulfonamide); consider an alternate NSAID
  - Duplicate NSAID use is possible; consider using prescription doses of ibuprofen
  - Counsel the patient to not abruptly discontinue duloxetine use and to monitor her mood; recommend seeking help from a parent or adult if negative thoughts or self-harm occur
  - All of the above

## References

1. Harrop, J.E., Management of Pain in Childhood, Arch Dis Child-Education and Practice, 2007; 92: 101-108.
2. Beggs, S., Fitzgerald, M., Development of peripheral and spinal nociceptive systems, In: Anand, KJS, Stevens, B.J., McGrath, P.J., eds., Pain in Neonates and Infants. 3<sup>rd</sup> edition, Edinburg, United Kingdom: Elsevier, 2007.
3. Drendel, A.L., Brousseau, D.C., Gorelick, M.H., Pain assessment for pediatric patients in the emergency department, Pediatrics 2006, 117, 1511-1518.
4. Ali, S., Drendel, A.L., Kircher, J., Beno, S., Pain management of musculoskeletal injuries in children: current state and future directions, Pediatric Emergency Care, July 2010, 26(7): 518-24.
5. American Pain Society, Pediatric Chronic Pain, [www.ampainsoc.org/advocacy/pediatric.htm](http://www.ampainsoc.org/advocacy/pediatric.htm), Jan. 17, 2010.
6. ICSI Health Care Guideline: Assessment and Management of Acute Pain, 6<sup>th</sup> edition/March 2008, [www.icsi.org](http://www.icsi.org).
7. Meighen, K.G., J Child Duloxetine treatment of pediatric chronic pain and co-morbid major depressive disorder, Adolesc Psychopharmacol, February 2007, 17(1): 121-7.
8. Cornelissen, P., Van Kleef, M., Nagy, M., Day, M., Zundert, J.V., Evidence based interventional pain practice according to diagnosis: Persistent idiopathic facial pain, Pain Practice, Oct. 27, 2009, DOI: 10.1111/j.1533-2500.2009.00332.
9. Nayak, S., Cunliff, M., Lidocaine 5% patch for localized chronic neuropathic pain in adolescents: report of five cases, Pediatric Anesthesia 2008, 18: 554-558.
10. Tutag Lehr, V., BeVier, P. "Make the Pain Go Away" Pediatric Pain Management: Update for Pharmacists, Part I: Pain Assessment and Opioid Analgesics, Michigan Pharmacist, March/April 2011, Vol. 49, [www.michiganpharmacists.org](http://www.michiganpharmacists.org).
11. Smith, H.S., Bracken, D., Smith, J.M., Pharmacotherapy for fibromyalgia, [www.frontiersin.org](http://www.frontiersin.org), March 31, 2011.
12. Weinreb, H.J., Managing chronic non-malignant pain: Overcoming obstacles to the use of opioids, Advances in Therapy, 2000, 17(2): 70-83.
13. Eisenberg, E., McNichol, E., Carr, D.B., Opioids for neuropathic, Cochrane Database Syst Rev, July 19, 2006, 3:CD006146.
14. Noble, M., Treadwell, J.R., Treager, S.J. et al., Long-term opioid management for chronic non-cancer pain, Cochrane Database Syst Rev, Jan. 20, 2010, 1:CD006605.
15. Peng, P., Simpson, J.N., Choiniere, M. et al., Dedicated multidisciplinary pain management centres for children in Canada: the current status, Canadian J Anesthesia 2007, 54; 963-968.
16. Gil, K.M., Family pain history predicts child health status in children with chronic rheumatic disease, Pediatrics 2001, 108; e47.
17. Kashikar-Zuck, S., Parkins, I.S., Ting, T.V. et al., Controlled follow-up study of physical and psychosocial functioning of adolescents with juvenile primary fibromyalgia syndrome, Rheumatology 2010, 49: 2204-2209.
18. Amouroux, R., Rousseaux-Salvador, C., Anxiety and depression in children and adolescents with migraine: a review of the literature, Encephale, October 2008, 34(5): 504-10.
19. Walco, G., Dworkin, R.H., Krane, E.J., LeBell, A.A., Treede, R.D., Neuropathic pain in children: Special considerations, Mayo Clin Proc 2010; 85(3)(suppl): S33-S41.
20. Baron, R., Neuropathic Pain: A clinical perspective, In : B.J. Canning and D. Spina (eds.), Sensory Nerves, 3 Handbook of Experimental Pharmacology 194, DOI: 10.1007/978-3-540-79090-7\_1, # Springer-Verlag Berlin Heidelberg 2009

21. Jacob, E., Neuropathic pain in children with cancer, *Journal of Pediatric Oncology Nursing* 2004; 21(6): 350-356.
22. Hershey, A.D., Winner, P., Pediatric Migraine *JAOA* 2005; 105(4)Suppl 2 (4): S2-S8.
23. Balasubramaniam, R., Arava-Prastatidis, M., Neuropathic orofacial pain in children and adolescents, *Pediatric Dentistry* 2008.
24. Grazzi, L., Usai, S., Rigamonti, A., Facial pain in children and adolescents, *Neurological Science* 2005; 26: S103.
25. Arruda, M.A., Albuquerque, A.P., Bigal, M.E., Uncommon headache syndromes in the pediatric population, *Current Pain Headache Reports*, March 15, 2011.
26. Anthony, K.K., Schanberg, L.E., Juvenile primary fibromyalgia syndrome, *Current Rheumatology Reports* 2001, 3(2): 165-171.
27. Sumpton, J.E., Moulin, D.E., Fibromyalgia: Presentation and management with a focus on pharmacological treatment, *Pain Res Management* 2008, 13(6): 477-483.
28. Low, A.K., Ward, K., Wines, A.P., Pediatric complex regional pain syndrome, *J Pediatric Orthopedics* 2007, 27(5): 567-572.
29. Kearns, G.L., Abel-Rahman, S.M., Alander, S.W., et al., Developmental pharmacology, *New England Journal of Medicine*, 2002.
30. Anand, K.J.S., Aranda, J.V., Berde, C.B., Buckman, S., Capparelli, E.V., Carlo, W., Hummel, P., Lantos, J., Johnston, C.C., Tutag Lehr, V., Lynn, A.M., Maxwell, L.G., Oberlander, T., Raju, T.N.K., Soriano, S., Taddio, A., Walco, G.A., Analgesia for Neonates: Study Design and ethical issues, *Clin Ther* 2005, 27: 814-843.
31. World Health Organization, *Cancer Pain Relief*, Geneva, 1996.
32. Tutag Lehr, V., BeVier, P., Patient controlled analgesia for the pediatric patient, *Orthopedic Nursing*, 2003 July/Aug, 22(4): 298-306.
33. Children's Hospital of Michigan Analgesic Dosing Guidelines: Department of Pharmacy and Pain Management Service, October 2010.
34. Beutler, A.I., et al., *Am Fam Physician*, FPIN's Clinical Inquiries, Aspirin use in children for fever or viral syndromes, Dec. 15, 2009, 80(12): 1472.
35. Clark, E., Plint, A.C., Correll, R. et al., A randomized, controlled trial of acetaminophen ibuprofen and codeine for acute pain relief in children with musculoskeletal trauma, *Pediatrics* 2007; 119: 460-67.
36. Morton, N.S., Prevention and control of pain in children, *British Journal of Anaesthesia*, 1999, 83(1): 118-129.
37. Berde, C.B., Sethna, N.F., Analgesics for the treatment of pain in children: Drug therapy, *New England Journal of Medicine*, 2002, 347(14): 1094-110.
38. Wilson, J.T., Tutag Lehr, V., Crane, E., Antipyretics, In: Yaffe, S.J., Aranda, J.V., eds. *Pediatric Pharmacology: Therapeutic Principles in Practice*, 4<sup>th</sup> edition, Philadelphia, PA: Lippincott, Williams & Wilkins, 2010: 598-609.
39. Hamalamen, M.I., Hoppo, K., Valkeika, E. et al., Ibuprofen or acetaminophen for the acute treatment of migraine in children: a double-blind, randomized, placebo controlled crossover study, *Neurology* 1997, 48: 103-107.
40. Bertin, L., Penns, G., d' Artis et al., Randomized double-blind, multi-center, controlled trial of ibuprofen versus acetaminophen (paracetamol) and placebo for treatment of symptoms of tonsillitis and pharyngitis in children, *J Pediatr* 1991, 119: 811-814.
41. American Academy of Pediatrics Committee on Drugs, Acetaminophen toxicity in children. *Pediatrics* 2001, 108 (4)1020-1024.
42. Taketomo, Hodding, Kraus Eds. *Pediatric Dosage Handbook*. 17<sup>th</sup> edition, Hudson, Ohio, Lexi-Comp: 2010, pp. 36-39.

43. Ardein, S.P., Sunday, J.S., Update on nonsteroidal anti-inflammatory drugs, *Curr Opin Rheumatol* 2006, 18(3)221-226.
44. Ketorolac, Taketomo, Hodding, Kraus Eds. *Pediatric Dosage Handbook*, 17<sup>th</sup> edition, Hudson, Ohio, Lexi-Comp: 2010, pp. 781-785.
45. Fletcher, J.T., Graf, N., Scarman, A., Saleh, H., Alexander, S.I., Nephrotoxicity with cyclooxygenase 2 inhibitor use in children, *Pediatr Nephrol* 2006, 21: 1893-1897.
46. Levy, D.M., Imundo, L.F., *Nonsteroidal Anti-Inflammatory Drugs: A survey of practices and concerns of pediatric medical and surgical specialists and a summary of available safety data*, *Pediatric Rheumatology* 2010.
47. Taketomo, Hodding, Kraus Eds. *Pediatric Dosage Handbook*, 17<sup>th</sup> edition, Hudson, Ohio, Lexi-Comp: 2010, pp. 279-281.
48. Taketomo, Hodding, Kraus Eds. *Pediatric Dosage Handbook*, 17<sup>th</sup> edition, Hudson, Ohio, Lexi-Comp: 2010, pp. 1307-1308.
49. Tutag Lehr, V., Ryckman, J., Gaynor, K., Thomas, R., Mattoo, T.K., Experience with ketorolac analgesia in hospitalized children less than two years of age, *E-PAS2011*:1499:532.
50. A Burd et al., Heterotopic ossification prophylaxis with indomethacin increases the risk of long-bone nonunion, *J Bone Joint Surg B*, 2003, 85: 700-705.
51. Reuben, S.S., Effect of nonsteroidal anti-inflammatory drugs on osteogenesis and spinal fusion, *Reg Anesth Pain Med* 2001, 26: 590-1.
52. Patzter, L., Nephrotoxicity as a cause of acute injury in children, *Pediatric Nephrology* 2008, 23: 2159-2173.
53. Pilotto, A., Serpia, D., Franceschi, M. et al., Genetic susceptibility to nonsteroidal anti-inflammatory drug-related gastroduodenal bleeding: role of cytochrome P450 2C9, *Polymorphisms Gastroenterology* 2007, 133: 465-473.
54. Sullivan, J.E. et al., *American Academy Pediatrics Clinical Guidelines: Fever and antipyretic use in children*, *Pediatrics* 2011, 127(3): 580-587.
55. Cuzzolin, L., Cerz, M.D., Fanos, V., NSAID-Induced nephrotoxicity from the fetus to child, *Drug Safety* 2001, 24(1): 9-18.
56. Hepatotoxicity related to antirheumatic drugs, *Nat Rev Rheumatol*, Mar 7, 2011, (3): 139-150.
57. Chemtob, S., Dorval, V.G., Non-steroidal anti-inflammatory drugs, In: Yaffe, S.J., Aranda, J.V., eds., *Pediatric Pharmacology: Therapeutic Principles in Practice*, 4<sup>th</sup> edition Philadelphia, PA: Lippincott, Williams & Wilkins, 2010: 711-721.
58. Otto, M., Bach, F.W., Jensen, T.S. et al., Escitalopram in painful polyneuropathy: a randomized, placebo-controlled, cross-over trial, *Pain* 2008, 139: 275-283.
59. Fishbain, D.A., Cutler, R., Rosomoff, H.L., Rosomoff, R.S., Evidence-based data from animal and human experimental studies on pain relief with antidepressants: a structured review, *Pain Med* 2000, 1: 310-316
60. Meighen, K.G., Duloxetine treatment of pediatric chronic pain and co-morbid major depressive disorder, *J Child Adolesc Psychopharmacol* 2007.
61. Desarkar, P., Das, A., Sinha, V.K., Duloxetine for childhood depression with pain and dissociative symptoms, *European Child Adolescent Psychiatry* 2006; 15(8): 496-499.
62. Amitriptyline, Taketomo, Hodding, Kraus Eds. *Pediatric Dosage Handbook*, 17<sup>th</sup> edition, Hudson, Ohio, Lexi-Comp: 2010, pp. 279-281.
63. Nortriptyline, Taketomo, Hodding, Kraus Eds. *Pediatric Dosage Handbook*, 17<sup>th</sup> edition, Hudson, Ohio, Lexi-Comp: 2010, pp. 279-281.
64. Greco, C., Management of chronic adolescent chronic pelvic pain from endometriosis: a pain center experience, *J Pediatr Adolescent Gynecol* 2005; 16(3): Suppl, S17-S19.
65. Food and Drug Administration, [www.fda.gov/Drugs/DrugSafety/UCM085729](http://www.fda.gov/Drugs/DrugSafety/UCM085729).

66. Tutag Lehr, V., Chugani, H., Aranda, J.V., Anticonvulsants, In: Yaffe, S.J., Aranda, J.V., eds. *Pediatric Pharmacology: Therapeutic Principles in Practice*, 4<sup>th</sup> edition, Philadelphia, PA: Lippincott, Williams & Wilkins, 2010: 533-551.
67. Vandracek, P., Oslejskova, H., Kepak, T. et al., Efficacy of pregabalin in neuropathic pain in paediatric oncological patients, *European Journal Paediatric Neurology* 2009, 13: 332-336.
68. Ferraro, D., DiTrapani, G., Topiramate in the prevention of pediatric migraine: literature review, *J Headache Pain* 2008, 9(3): 147-150.
69. Adelman, J., Freitag, F.G., Lainez, M. et al., Analysis of safety and tolerability data obtained from over 1,500 patients receiving topiramate for migraine prevention in controlled trials, *Pain Med* 2008, (2):175-185.
70. Malaga, I., Sanmarti, F.X., Two cases of painful gynecomastia and lower extremity pain associated with pregabalin therapy, *Epilepsia* 2006, 47(9): 1576-1579.
71. Argoff, C.E., Conclusions: chronic pain studies of lidocaine patch 5% using the Neuropathic Pain Scale, *Current Medical Research and Opinion* 2004, 20: S2: S29-S31.
72. Campbell, B.J., Rowbotham, M., Davies, P.S. et al., Systemic absorption of topical lidocaine in normal volunteers, patients with post-herpetic zoster, neuralgia and patients with acute herpes zoster, *J Pharm Sci* 2002, 91(5): 1343-1350.
73. Lidocaine, Taketomo, Hodding, Kraus Eds. *Pediatric Dosage Handbook*, 17<sup>th</sup> edition, Hudson, Ohio, Lexi-Comp: 2010, pp. 818-821.