Analgesics and Anti-inflammatory Medications in Sports: Use and Abuse

Cynthia L. Feucht, PharmD, BCPS[a,b,*],
Dilip R. Patel, MD, FAAP, FACSM, FAACPDM, FSAM[b,c]

KEYWORDS

• Musculoskeletal injury • Nonsteroidal anti-inflammatory drugs
• Acetaminophen • Topical analgesics • Sports

Musculoskeletal injuries account for most sports-related injuries.[1] Overuse musculoskeletal injuries account for more than half of all sport-related injuries in adolescents and young adults. Overuse injuries can result in chronic or intermittent symptoms depending on the athlete's level of activity. Acute muscle injuries (strains, contusions, and lacerations) can lead to significant structural or functional damage to the muscle.[1–11] Delayed-onset muscle soreness (DOMS) (exercise-induced muscle damage [EIMD]), typically associated with new or unaccustomed exercise, often results from intense eccentric muscle activity and manifests with pain, discomfort, and decreased performance 24 to 48 hours after exercise.[1,4]

Nonpharmacological approaches are often considered as first-line treatment for musculoskeletal injuries and may include relative rest, ice, compression, and elevation.[3] Moderate to severe injuries to the athlete may result in several weeks of an inability to train or compete. Even after resuming the physical activity or sport, the athlete may continue to experience difficulties with muscle weakness and decreased flexibility.[1] As a result, treatment is often sought to alleviate pain, restore function, and allow the athlete to resume activities more quickly. Treatment options include analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and topical over-the-counter (OTC) preparations. These classes of drugs are reviewed in this article, including their mechanisms of action, side effects, and efficacy in treating pain and inflammation associated with acute and overuse musculoskeletal injuries.

[a] Department of Pharmacy Practice, Ferris State University, Kalamazoo, MI, USA
[b] MSU/KCMS, 1000 Oakland Drive, Kalamazoo, MI 49008, USA
[c] Department of Pediatrics and Human Development, Michigan State University College of Human Medicine, East Lansing, MI, USA
* Corresponding author. MSU/KCMS, 1000 Oakland Drive, Kalamazoo, MI 49008.
E-mail address: cynthia.feucht@gmail.com

Pediatr Clin N Am 57 (2010) 751–774
doi:10.1016/j.pcl.2010.02.004 **pediatric.theclinics.com**
0031-3955/10/$ – see front matter

MECHANISM OF ACTION

Arachidonic acid is released from cellular membranes as a result of tissue injury. Arachidonic acid is broken down by cyclooxygenase (COX) to produce prostaglandins and thromboxane A_2, and by lipoxygenase (LOX) enzymes to produce leukotrienes. Prostaglandins are localized hormones that, once released within the intracellular space, can produce fever, inflammation, and pain.[12] Thromboxanes are released in response to tissue injury and are responsible for producing platelet aggregation and clot formation, and for regulation of vascular tone.[12] Pain relief and decreased inflammation occur from the blockade of COX enzymes, thereby inhibiting prostaglandin E_2 and prostacyclin (PGI_2) formation (**Fig. 1**).[12,13]

Two forms of COX enzymes are cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is expressed in most normal tissues and cells, and is the predominant form within gastric epithelial cells.[12,14] Prostaglandin production within the gastrointestinal tract protects the gastrointestinal mucosa from gastric acidity. COX-2 is expressed when tissue damage occurs, and its release is induced by cytokines and inflammatory mediators during inflammation.[12,14]

NSAIDs are a heterogeneous class of medications that are chemically unrelated but known to have similar therapeutic effects, including antipyretic, analgesic, and anti-inflammatory activity. Their primary therapeutic effect is due to inhibition of prostaglandin synthesis by inhibiting COX-2 activity, and a correlation exists between COX-2 inhibition and anti-inflammatory activity.[15] Bradykinin and cytokines (ie, tumor necrosis factor-α [TNF-α] and interleukin-1 [IL-1]) are thought to be responsible for inducing pain with inflammation and releasing prostaglandins that enhance pain sensitivity.[16] Other mediators, such as neuropeptides (ie, substance P) are also involved in inducing pain. The gastrointestinal adverse effects of NSAIDs are predominantly, but not exclusively, due to inhibition of COX-1 enzyme (**Fig. 2**). NSAIDs are considered

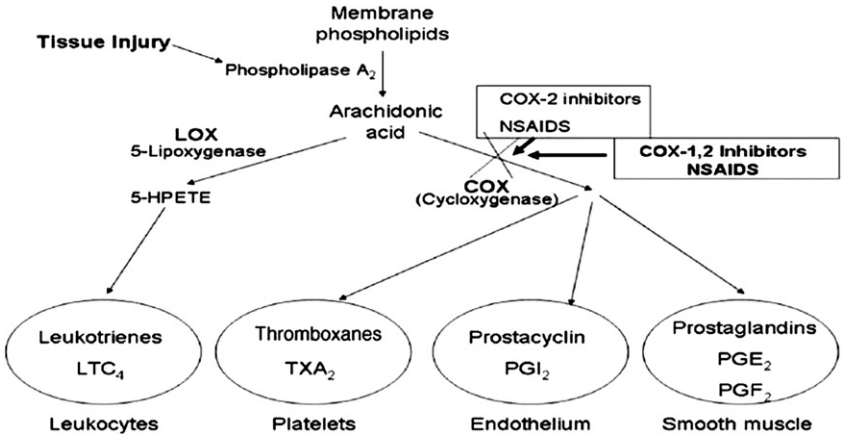

Fig. 1. When a cell membrane is injured, the arachidonic acid pathway is activated to initiate the local inflammatory response through the production of prostaglandins, thromboxanes, and leukotrienes. Their activation, however, requires the enzymes COX and LOX. The NSAIDs can block COX action and thereby prevent the formation of the COX-derived inflammatory mediators. 5-HPETE, 5-hydroperoxyeicosatetraenoic acid; LTC_4, leukotriene C4; PGE_2, prostaglandin E2; PGF_2, prostaglandin F2; PGI_2, prostacyclin; TXA_2, thromboxane. (*From* Maroon J, Bost J, Borden M, et al. Natural anti-inflammatory agents for pain relief in athletes. Neurosurg Focus 2006;21(4):E11; with permission.)

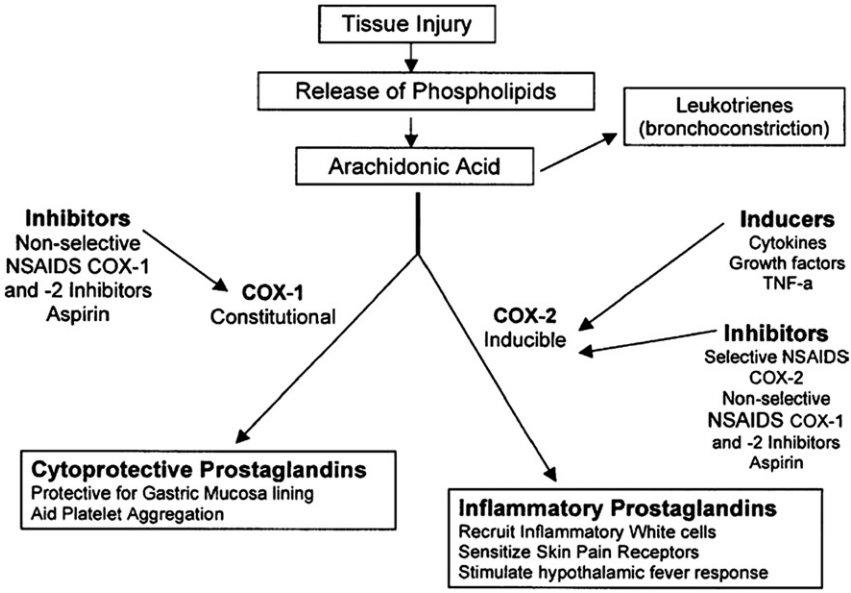

Fig. 2. The COX enzyme can exist in 2 forms: COX-1, constitutional or existing in small amounts at all times; or COX-2, inducible or only present during the inflammatory response. By selectively blocking only the COX-2–produced inflammatory prostaglandins, COX-2–inhibiting medications were believed to be superior to nonselective COX-1 and -2 inhibitors, and they were thought to have fewer gastric side effects. (*From* Maroon J, Bost J, Borden M, et al. Natural anti-inflammatory agents for pain relief in athletes. Neurosurg Focus 2006;21(4):E11; with permission.)

competitive, reversible inhibitors of COX enzymes (unlike aspirin, which is considered an irreversible inhibitor of COX enzymes) and do not affect the LOX pathway.[17]

SALICYLATED NSAIDS

Derivatives of salicylic acid include aspirin (acetylsalicylic acid), diflunisal (difluorophenyl derivative), salsalate, magnesium salicylate, and choline magnesium salicylate (**Tables 1** and **2**). Aspirin continues to be the most widely used drug and is the standard to which other NSAIDs are compared.[18] Due to its widespread availability, aspirin's potential for toxicity often goes underrecognized, and it continues to be a cause of fatal poisonings in children.[14]

Salicylates are rapidly absorbed from the gastrointestinal tract, are widely distributed throughout the body, and are highly protein bound (especially albumin).[16] Due to their high protein binding, salicylates may compete for binding with other compounds, including thyroxine, penicillin, phenytoin, bilirubin, uric acid, and other NSAIDs such as naproxen.[14] Salicylates are metabolized in the liver and excreted by the kidneys, with free salicylate excretion dependent on urinary pH and salicylate dose.[16]

Gastrointestinal adverse effects are common with salicylates and may include dyspepsia, nausea, vomiting and, more seriously, gastric ulceration, gastrointestinal hemorrhage, and erosive gastritis.[14,16] Aspirin irreversibly inhibits platelet aggregation and leads to a prolongation in the bleeding time. Gastrointestinal and platelet effects

Table 1
Salicylated NSAIDs

Drug	Onset of Action and Duration of Effect (hours)	Comments
Diflunisal	Onset: ~1 Duration: Analgesic: 8–12 Anti-inflammatory: ≤12	~4–5 times more potent analgesic and anti-inflammatory effects than aspirin; fewer platelet/GI side effects compared with aspirin; not metabolized to salicylic acid
Salsalate	Onset: N/A Duration: N/A	Fewer platelet and GI side effects than aspirin
Choline magnesium trisalicylate	Onset: ~2 Duration: N/A	Less effect on platelet aggregation and fewer GI side effects than aspirin; avoid or use with caution in renal insufficiency due to magnesium content
Magnesium salicylate	Onset: N/A Duration: 4–6	Available OTC; less effect on platelet aggregation and fewer GI side effects than aspirin; avoid or use with caution in renal insufficiency due to magnesium content

Abbreviations: GI, gastrointestinal; N/A, no data available; OTC, over-the-counter.
Data from Refs.[13,14,40]

are less likely to occur with nonacetylated salicylates (ie, salsalate, magnesium salicylate, and so forth) because they cannot acetylate COX.[16] Owing to aspirin's effect on platelet aggregation, it should be avoided in patients with hepatic impairment, hypoprothrombinemia, vitamin K deficiency, hemophilia, and within 1 week of a surgical procedure.[14]

Salicylates have been shown to have a dose-dependent effect on uric acid excretion, and in elevated doses can result in pulmonary edema, hepatotoxicity, and hyperglycemia.[14] Hypersensitivity to salicylates can result in hives, flushing, bronchoconstriction, angioedema, low blood pressure, and shock.[14] Hypersensitivity is thought to be due to COX inhibition, and cross-sensitivity occurs with other agents in the class as well as with nonsalicylated NSAIDs.[14] Patients with asthma, nasal polyps, and sensitivity to tartrazine dyes are at an increased risk for salicylate sensitivity.[19] In general, salicylates are avoided during pregnancy, especially the third trimester, due to an increased risk for perinatal death, anemia, antepartum and postpartum hemorrhage, prolonged gestation, and premature closure of the ductus arteriosus.[14]

Drug interactions can occur from salicylates displacing other agents from plasma-binding proteins. Dosages of NSAIDs, sulfonylureas, and methotrexate may need to be adjusted to prevent toxicity due to displacement. NSAIDs given concurrently with corticosteroids and warfarin may increase the risk for bleeding. NSAIDs should not be given concomitantly with the following herbals due to their anticoagulant or antiplatelet activity and increased risk for bleeding: danshen, dong quai, evening primrose, feverfew, garlic, ginger, ginkgo, red clover, horse chestnut, green tea,

Table 2
Common doses of salicylated NSAIDs

Generic Name	Trade Name	Adult Dose	Comments
Diflunisal		1000 mg, then 500 mg every 12 h Age ≥12 y: same as adult	Do not crush or chew tablet; maximum 1.5 g daily
Salsalate	Amigesic	1 g 3 times daily	Do not crush tablets; urinary acidification can decrease clearance and increase risk for toxicity
Choline magnesium trisalicylate	Trilisate	500 mg–1.5 g 2–3 times daily	Maintenance dose: 1–4.5 g daily; available as liquid formulation; urinary acidification can decrease clearance and increase risk for toxicity
Magnesium salicylate	Doan's Extra Strength Keygesic	Doan's (467 mg): 2 caplets every 6 h as needed Keygesic (650 mg): 1 tablet every 4 h as needed Age ≥12 y: same as adult	Available OTC; Doan's: maximum 8 caplets in 24 h Keygesic: maximum 4 tablets in 24 h

Data from Refs.[19,40]

policosanol, and willowbark.[19,20] In addition, NSAIDs decrease the effectiveness of angiotensin-converting enzyme (ACE) inhibitors because of the blockade of renal prostaglandin production.

Salicylates have fallen out of favor for use in adolescents and young adults because of their association with Reye syndrome. Reye syndrome is characterized by toxic hepatitis and has been associated with encephalopathy, prolonged prothrombin time, fatty infiltration of the liver, and intracranial hypertension in advanced stages.[21] Aspirin and other salicylates are contraindicated in children and young adults younger than 20 years who have a fever associated with a viral illness.[14]

NONSALICYLATED NSAIDS

Various classes of nonsalicylated NSAIDs (**Tables 3** and **4**) are among the most widely used drugs, with yearly sales in the United States for OTC drugs estimated at $30 billion.[13,22] Nonsalicylated NSAIDs are considered effective for mild to moderate pain, and have been used for a variety of musculoskeletal disorders including osteoarthritis, rheumatoid arthritis, and sports-related injuries. The choice of a particular nonsalicylated NSAID depends on its onset of action, tolerability, cost, and insurance coverage. An agent with a short onset of action, minimal adverse effects, low cost, and wide acceptability would make for an ideal nonsalicylated NSAID.

Table 3
Nonsalicylated NSAIDs

Drug	Onset of Action and Duration of Effect	Comments
Propionic acids		
Fenoprofen	Onset: ~72 h Duration: 4–6 h	~15% of patients will have side effects but few stop therapy
Flurbiprofen	Onset: ~1–2 h Duration: variable	Strong inhibitor of CYP 450 2C9 isoenzyme; substrate CYP 2C9 (minor)
Ibuprofen	Onset: Analgesic: 0.5–1 h Anti-inflammatory: ≤7 d Duration: 4–6 h	Strong inhibitor of CYP 450 2C9 isoenzyme; substrate CYP 2C9 and 2C19 (minor); equal efficacy to aspirin; ~10%–15% of patients stop therapy due to side effects
Ketoprofen	Onset: 0.5 h Duration: 6 h	~30% of patients develop side effects with GI as the most common
Naproxen	Onset: Analgesic: 1 h Anti-inflammatory: 2 weeks Duration: Analgesic: ≤7 h Anti-inflammatory: ≤12 h	Available as OTC product; more potent than aspirin in vitro, likely better tolerated than aspirin; may provide cardioprotection for some individuals with heart disease
Oxaprozin	Onset: ~0.5–4 h Duration: variable	Slower onset of effects compared with others; longer half-life allows for once a day dosing
Acetic acids		
Diclofenac	Onset: 1–4.5 h Duration: 12–24 h	More potent than aspirin; side effects experienced by ~20% and 2% stop therapy; ~15% of patients will experience an increase in liver function test; available as topical patch and gel as well as in combination with misoprostol
Etodolac	Onset: Analgesic: 2–4 h Anti-inflammatory: several days Duration: N/A	In vitro COX-2 selectivity; 100 mg of etodolac provides similar efficacy to aspirin 650 mg but may have fewer side effects
Sulindac	Onset: N/A Duration: N/A	Similar efficacy to aspirin; active metabolite; side effects experienced ~20% GI and ~10% CNS

Tolmetin	Onset: Analgesic: 1–2 h Anti-inflammatory: days to weeks Duration: variable	Similar efficacy to aspirin; side effects experienced by ~25%–40% and 5%–10% stop therapy
Indomethacin	Onset: ~0.5 h Duration: 4–6 h	Compared with aspirin10–40 times more potent; incidence of side effects 3%–50%; ~20% of patients stop therapy due to side effects
Ketorolac	Onset: Analgesic: ~10 min (IM) Duration: Analgesic: 6–8 h	Maximum duration of 5 d (oral and parenteral); strong analgesic activity but weak anti-inflammatory activity; may be given parenterally for acute pain
Oxicams		
Meloxicam	Onset: N/A Duration: N/A	CYP 450 inhibitor of isoenzyme 2C9 (weak); substrate CYP 2C9 and 3A4 (minor); some COX-2 selective action at lower end of dosing range
Piroxicam	Onset: ~1 h Duration: variable	Equal efficacy to aspirin; may be better tolerated than aspirin; ~20% of patients will experience side effects and 5% will stop therapy
Naphthylalkanone		
Nabumetone	Onset: ~72 h Duration: variable	Prodrug; some COX-2 selectivity; has less GI toxicity than most NSAIDs
Fenamate		
Meclofenamate	Onset: <1 h Duration: $\leq$6 h	Equal efficacy to aspirin; ~25% of patients will experience gastrointestinal adverse events
Mefenamic acid	Onset: N/A Duration: $\leq$6 h	CYP 450 inhibitor of isoenzyme 2C9 (strong); substrate CYP 2C9 (minor)
COX-2 inhibitor		
Celecoxib	Onset: Analgesic: ~0.75 h to several months Duration: ~4–8 h	CYP 450 inhibitor of isoenzymes 2C8 (moderate) and 2D6 (weak); substrate CYP 2C9 (major) and 3A4 (minor); does not inhibit platelet aggregation

Data from Refs.[13,14,40]

Table 4
Common doses of nonsalicylated NSAIDs

Generic Name	Trade Name	Adult Dose	Comments
Propionic acids			
Fenoprofen	Naflon	200 mg every 4–6 h as needed	Maximum: 3.2 g/d; do not crush tablets
Flurbiprofen	Ocufen	50–100 mg 2–3 times daily	Maximum: 300 mg/d; maximum single dose100 mg; do not crush tablets
Ibuprofen	Motrin Advil	200–400 mg every 4–6 h Maximum: 3.2 g/d	Available OTC; available in tablet (regular and chewable), capsule, suspension and infant drops; chewable tablets may contain phenylalanine
Ketoprofen	Oruvail	25–50 mg every 6–8 h as needed	Extended-release formulation is not recommended for acute pain; maximum (immediate release) 300 mg/d; maximum (extended release): 200 mg/d
Naproxen sodium	Aleve Anaprox Anaprox DS	500 mg initially, then 250 mg every 6–8 h as needed OTC label: 200 mg every 8–12 h as needed	Available OTC; dosage recommendations expressed as naproxen base; maximum (adult): 1250 mg/d (naproxen base); OTC formulation not indicated for age <12 y
Naproxen	Naprosyn Naprelan	500 mg initially, then 250 mg every 6–8 h as needed	Available as immediate-release, extended-release and suspension; extended release not recommended for acute pain; do not break, crush, or chew extended-release formulation; maximum (adult): 1250 mg/d
Oxaprozin	Daypro	600–1200 mg daily	Patients with low body weight should start with 600 mg daily; do not crush tablets
Acetic acids			
Diclofenac	Voltaren	50 mg 3 times daily	Available as immediate, extended-release formulation and powder for solution; do not crush or chew tablets; mix powder in 30–60 mL of water and drink immediately; maximum: 200 mg daily
Diclofenac patch	Flector patch	Apply 1 patch twice daily	Apply patch to most painful area of intact skin; wash hands after applying and after removal; may tape edges of patch if peeling occurs; do not wear while sunbathing; fold used patches before disposal

Etodolac	Lodine	200–400 mg every 6–8 h	Maximum: 1000 mg daily (immediate-release) and 1200 mg daily (extended-release); available as immediate- and extended-release formulation; do not crush tablets or break capsules
Sulindac	Clinoril	150–200 mg twice daily	Maximum: 400 mg daily
Tolmetin	Tolectin	400 mg 3 times daily	Maximum: 1800 mg daily; taking with food decreases bioavailability; do not crush tablets or break capsules
Indomethacin	Indocin	25–50 mg 2–3 times daily Age $\geq$15 y: same as adult	Available as immediate- and extended-release capsules and suspension; maximum (adult): 200 mg/d (immediate-release) and 150 mg/d (extended-release); do not crush, break or chew capsules
Ketorolac	Toradol	20 mg, then 10 mg every 4–6 h as needed <50 kg: 10 mg, then 10 mg every 4–6 h as needed	Not to exceed 5 d in duration (injection and oral combined); maximum: 40 mg daily; oral dosing intended to be a continuation of IM/IV therapy; not indicated for minor or chronic pain conditions
Oxicams			
Meloxicam	Mobic	7.5–15 mg once daily	Available as oral suspension
Piroxicam	Feldene	10–20 mg once daily	Maximum: 20 mg/d; do not break capsules
Naphthylalkanone			
Nabumetone	Relafen	1000 mg daily in 1–2 divided doses	Maximum: 2 g/d; do not crush tablets
Fenamate			
Meclofenamate		50–100 mg every 4–6 h as needed Age >14 y: same as adult	Maximum: 400 mg/d
Mefenamic acid	Ponstel	500 mg, then 250 mg every 4 h as needed Age >14 y: same as adult	Maximum duration: usually 1 week
COX-2 inhibitor			
Celecoxib	Celebrex	200 mg twice daily as needed	Contents of capsule may be sprinkled onto applesauce for administration; poor metabolizers of CYP 2C9 start at half the recommended dose

Data from Refs.[19,40]

As a class, nonsalicylated NSAIDs are usually well absorbed and highly bound to plasma proteins, and are excreted via either glomerular filtration or tubular secretion.[14] These agents accumulate at sites of inflammation, and most exhibit nonselectivity for COX-1 and COX-2 enzymes. The last decade has seen the emergence of COX-2 selective inhibitors designed to minimize gastrointestinal effects that occur due to COX-1 inhibition. Other older nonsalicylated NSAIDs have also been found to have COX-2 selectivity similar to the currently available celecoxib, based on whole blood assays.[14] Most studies on nonsalicylated NSAIDs are done in adults; however, some findings are of relevance to the adolescent age group.

SIDE EFFECTS OF NONSALICYLATED NSAIDS

Gastrointestinal

Gastrointestinal adverse effects are common with nonsalicylated NSAIDs and are often the leading reason for their discontinuation. The gastrointestinal toxicity is often dose dependent and associated with chronic use.[14] Dyspeptic symptoms are frequently experienced by patients and may include anorexia, epigastric pain, nausea, bloating, and heartburn. These symptoms have been associated with both selective and nonselective nonsalicylated NSAIDs.[13,23] Gastrointestinal toxicity may be related to prostaglandin inhibition, which is important for enhancing mucosal blood flow, mucus and bicarbonate production, and inhibition of acid production. Nonsalicylated NSAIDs also may contribute to gastrointestinal toxicity from local irritation to the gastric mucosa. More serious complications include gastric and duodenal ulcers, which may occur in up to 15% to 30% of regular nonsalicylated NSAID users.[24,25] Complications from ulcers include bleeding, perforation, and obstruction. Patients may present with a serious gastrointestinal event but have had no symptoms before presentation.[13] Factors that may increase the risk for gastrointestinal complications include the presence of *Helicobacter pylori*, advanced age, concomitant use of aspirin, anticoagulants, or corticosteroids, and duration of NSAID use (greatest within the first month).[13,26] Lifestyle factors such as smoking and alcohol use also contribute to an increased risk for side effects, but are not independent risk factors.[13,26] For those patients at risk, a proton pump inhibitor (PPI) has been shown to be effective at reducing the frequency and severity of upper gastrointestinal symptoms.[13,27]

COX-2 inhibitors were developed with the aim of reducing gastrointestinal complications associated with nonselective nonsalicylated NSAIDs. COX-2 inhibitors do not inhibit the COX-1 enzyme, which is responsible for prostaglandin production in the gastrointestinal mucosa, and therefore should have less risk for gastrointestinal toxicity. The benefit of COX-2 inhibitors with regard to less gastrointestinal toxicity remains controversial. In patients with gastrointestinal disease or risk factors for gastrointestinal complications, risk versus benefit should be assessed, and if nonsalicylated NSAIDs are used, the lowest dose for the shortest time period should be considered.[24,28]

Hepatotoxicity

Hepatotoxicity from NSAID use appears to be rare, with estimates between 3 and 23 cases per 10,000 patient years.[29,30] Two older agents (benoxaprofen and bromfenac) have been withdrawn in the United States due to reports of serious hepatotoxicity.[13] Rostom and colleagues,[31] in a systematic review, found the rate of hospitalization due

to nonsalicylated NSAID-related hepatotoxicity to be 2.7 per 100,000 patients and the rate of death to be 1.9 per 100,000 patients.

A recent case report by Bennett and colleagues[29] details a 16-year-old who was previously healthy and found to be taking ibuprofen for 6 weeks before presentation. The first 2 weeks of ibuprofen use was scheduled dosing and the subsequent 4 weeks was sporadic use. The adolescent presented with dark-colored urine, jaundice, and pruritus. Laboratory results were significant for an elevated bilirubin and minimal elevation in liver enzymes.[29] The results of a liver biopsy revealed intrahepatic and canalicular cholestasis.[29] Histology was suggestive of drug-induced hepatotoxicity.[29] Over the following 4 months, the patient's symptoms resolved and laboratory values returned to normal.

Liver dysfunction related to nonsalicylated NSAIDs is rare in otherwise healthy adolescents, but should be considered in a patient with recent nonsalicylated NSAID use and presenting with cholestasis.[29] Thorough medication histories are important in determining the cause and effect. Despite the potential for hepatotoxicity, current data do not support routine monitoring of liver enzymes in individuals receiving nonsalicylated NSAIDs.

Renal Toxicity

Renal insufficiency is well known with nonsalicylated NSAID use and is likely the result of inhibition of renal prostaglandins. Renal insufficiency is estimated to occur in approximately 1% to 5% of patients, and is usually reversible on discontinuation of the NSAID.[13,32] Renal prostaglandins serve an important role in maintaining renal circulation, including vasodilation, renin secretion, and sodium and water excretion.[13] The disruption in balance between vasoconstriction and vasodilation within the kidneys may predispose a patient to renal failure. Those at the greatest risk for renal toxicity associated with nonsalicylated NSAIDs include patients with heart failure, cirrhosis, chronic kidney disease, and hypovolemic states.[13,14] Renal toxicity is characterized by elevated serum creatinine, sodium and water retention, hyperkalemia, proteinuria, interstitial nephritis, papillary necrosis, acute renal failure, acute glomerulitis, vasculitis, acute tubular necrosis, and papillary necrosis.[13,33,34] In patients at risk for renal toxicity, the risk versus benefit in using a nonsalicylated NSAID should be carefully considered and, if at all possible, NSAIDs, including COX-2 inhibitors, should be avoided.

There have been several case reports of renal toxicity in adolescents with nonsalicylated NSAID use. Nakahura and colleagues[35] discuss 5 adolescents (13–19 years old) who developed renal toxicity with the use of nonsalicylated NSAIDs. The first case was a 16-year-old girl who took ibuprofen intermittently over 9 months. Kidney biopsy results were consistent with interstitial nephritis and the patient was treated with corticosteroids. At 1 year she was asymptomatic with a decrease in serum creatinine; however, 2 years later her serum creatinine had risen and results of a repeat kidney biopsy revealed chronic interstitial fibrosis.[35] Case 3 in this report describes a 15-year-old girl who used ibuprofen every other day for 6 months. The patient was found to have proteinuria, and results of renal ultrasonography were reported normal. The patient discontinued the nonsalicylated NSAID and was asymptomatic after 1 month.[35] The other 3 cases describe adolescents who used naprosyn (1 week before hospitalization), ibuprofen (daily use for several weeks), and ketorolac (intermittently for 4 months), who all developed an increase in serum creatinine and were found to have urine eosinophilia indicative of nonsalicylated NSAID-associated nephrotoxicity.[35] In 2 of the cases nephrotoxicity resolved, and the other case reported resolution of symptoms at 1 month but continued elevation in serum creatinine.

These case reports illustrate that nonsalicylated NSAID nephrotoxicity can occur in healthy adolescents. Given the fact that several nonsalicylated NSAIDs are available as OTC preparations, adolescents should be aware of their potential adverse effects. It is important to use the lowest dose of the nonsalicylated NSAID for the shortest time period necessary, and to maintain adequate hydration while on nonsalicylated NSAIDs.

Cardiovascular Toxicity

Cardiovascular toxicity related to nonsalicylated NSAID use is generally not of concern in otherwise healthy adolescents. Cardiovascular toxicity came to light with the emergence of the selective COX-2 inhibitors. It has been theorized that the disruption in the balance between prostacyclin and thromboxane formation by selective COX-2 inhibitors may increase this risk. The selective COX-2 inhibitors, via their inhibition of prostacyclin formation, favor increased thromboxane formation and subsequent platelet aggregation.

Current data suggest that selective nonsalicylated NSAIDs may increase cardiovascular risk, but data are conflicting.[24,36–38] Heterogeneity of the studies including patient selection, duration of study, agents used, study design, and cardiovascular risk at baseline makes it challenging to summarize the cardiovascular risks associated with nonsalicylated NSAIDs. Rofecoxib was voluntarily withdrawn from the United States market in September 2004, and the Food and Drug Administration (FDA) requested Pfizer to voluntarily remove valdecoxib from the market in April 2005 because of cardiovascular risks.[39] In addition, in 2005 the FDA requested the makers of prescription and OTC nonsalicylated NSAIDs to include a boxed warning highlighting the increased risk for cardiovascular events as well as gastrointestinal toxicity, including the risk for life-threatening gastrointestinal bleeding.[39]

Drug Interactions

Drug interactions are similar to those already described for salicylated NSAIDs as well as the following additional drug interactions. Nonselective nonsalicylated NSAIDs may decrease the effectiveness of aspirin if given concomitantly due to blockade of the platelet COX-1 site.[14] It is recommended that the nonsalicylated NSAIDs be given at least 2 hours after the dose of aspirin to achieve irreversible platelet inhibition by aspirin.[13] Nonsalicylated NSAIDs may also decrease the effectiveness of thiazide and loop diuretics through blockade of renal prostaglandins.[40] In addition, nonsalicylated NSAIDs can reduce renal clearance of lithium, resulting in elevated lithium plasma levels, and the efficacy of nonsalicylated NSAIDs can be reduced with cholestyramine and colestipol due to blockade of absorption.[40] Drug interactions can occur with mefenamic acid, celecoxib, meloxicam, ibuprofen, and flurbiprofen due to their metabolism via cytochrome P450 isoenzymes. With a wide variety of drug interactions, each patient's medication profile should be reviewed, including prescription, OTC, and herbal products, to evaluate for drug-drug interactions before initiating an nonsalicylated NSAID.

EFFICACY OF NSAIDS IN MUSCULOSKELETAL INJURIES

NSAIDs have been purported to help in decreasing pain and inflammation, restore musculoskeletal function, decrease time to healing, and allow faster return to previous activity level. The benefit of using NSAIDs in the prevention of myositis ossificans traumatica following deep muscle contusions remains controversial. Concern has been raised that by inhibiting the inflammatory response, NSAIDs may slow phagocytic

function and time for muscle regeneration and healing. Animal studies have been conflicting as to the effects of NSAIDs in the musculoskeletal model. Human studies have not always shown a consistent benefit of NSAIDs in treating musculoskeletal injuries. Studies have been limited at times by small sample sizes, lack of placebo group, subjective assessment, differing patient populations, and lack of control for confounding factors.

A recent review by Mehallo and colleagues[3] summarized data regarding use of NSAIDs for acute ligament and muscle injuries. Rat models for ligament sprains have shown that piroxicam strengthens the medial collateral ligament of the knee at 14 days versus celecoxib, which was found to weaken the medial collateral ligament at 14 days compared with placebo. Other animal studies have not found any benefit with selective and nonselective NSAIDs versus placebo.[3] Human studies have provided evidence for a more consistent benefit of NSAIDs in ligament sprains. A variety of NSAIDs have been shown to decrease pain and inflammation associated with acute ankle sprains.[3] Several studies have documented the efficacy of NSAIDs in decreasing pain, increasing functional ability, and allowing for a more rapid return to training.[3] Although NSAIDs have been shown to be effective for treating the pain associated with injured ligaments, their efficacy in improving joint stability remains unknown.[3] In 2 animal model studies, piroxicam was shown to improve contractile force and greater maximal failure force early post injury, but also slowed deposition of collagen and regeneration of muscle tissue.[3] Studies examining NSAIDs in human muscle strains are limited. One trial evaluated meclofenamate and diclofenac versus placebo along with physiotherapy in treating acute hamstring injuries, and found no differences among the groups with respect to pain, swelling, and isokinetic muscle performance.[3]

Howatson and van Someren[5] reviewed the use of NSAIDs in the treatment and prevention of DOMS. In one study, ketoprofen used prophylactically was found to decrease muscle soreness and enhance muscle function, while another study evaluated ibuprofen before and after exercise and demonstrated a decrease in muscle damage. In contrast, a study evaluated ibuprofen 45 minutes before downhill running and scheduled dosing for 3 days after the activity, and found no effect on muscle soreness or strength.[5] Additional studies with oxaprozin and ibuprofen with acetaminophen post exercise failed to provide benefit.[5] NSAIDs were found to attenuate loss of muscle strength and muscle soreness in 2 studies post exercise and in one study failed to provide evidence of benefit compared with placebo after elbow flexor eccentric muscle injury.[3] Conflicting evidence to support the use of NSAIDs in DOMS may be the result of differences in study methodology, patient selection, and study limitations. NSAIDs may provide benefit in decreasing muscle soreness and improving short-term muscle recovery.[3,41] Given the potential ability of NSAIDs to impair muscle healing, risk versus benefit should be considered and, if used, a short course of 3 to 7 days should be considered.[3]

TOPICAL NSAIDS

In addition to oral NSAIDs, topical formulations of NSAIDs have been used for treating musculoskeletal injuries. A systematic review conducted by Moore and colleagues[42] evaluated 37 placebo-controlled trials of topical NSAIDs in the treatment of acute soft tissue injury, sprains, strains, or trauma. Twenty-seven of the trials demonstrated a significant benefit of the topical NSAID over placebo.[42] The pooled relative benefit for all trials was 1.7 (95% confidence interval [CI]: 1.5–1.9).[42] For topical NSAIDs evaluated in 3 or more studies, pooling of data for the individual agents showed

ketoprofen, felbinac, ibuprofen, and piroxicam to be superior to placebo.[42] Local skin reactions were reported in 3% or fewer, systemic adverse effects in fewer than 1%, and discontinuation due to adverse effects in 0.6% or fewer, with no significant difference noted between active treatment and placebo groups.[42] The authors note that due to the small sample size of most of the trials, publication bias may have influenced the results of the systematic review.

Diclofenac gel and topical patch were the first topical NSAIDs approved in 2007 in the United States by the FDA. Diclofenac gel (Voltaren gel) is currently approved for treatment of osteoarthritis and diclofenac topical patch (Flector patch) for the treatment of acute minor sprains, strains, and contusions.[19] When applied to the skin, diclofenac accumulates under the application site, leading to a tissue reservoir for localized effects.[43] With its topical application, systemic plasma concentrations are in the range of 1 to 3 ng/mL and relative systemic bioavailability compared with oral administration is approximately 1%.[43] The diclofenac patch is relatively safe, with skin reactions as the most common adverse event.[43] Thus, the risk for systemic adverse effects is minimal due to low plasma concentrations.

A randomized, double-blind, placebo-controlled trial using topical diclofenac in ankle sprains found it to provide a greater reduction in pain on rest and movement from day 2 and faster joint swelling reduction from day 3.[44] Five percent of the patients in the placebo group discontinued treatment due to lack of efficacy compared with none in the topical diclofenac group.[44] Another randomized, double-blind, placebo-controlled study compared topical diclofenac to placebo in patients with traumatic blunt soft tissue injury.[44] Tenderness at the center of the injured area was produced by pressure applied from calibrated calipers. The primary end point was the area under the curve (AUC) for tenderness over the first 3 days of treatment.[44] The patch was found to be significantly more effective than placebo for the primary end point ($P<.0001$).[44] Topical diclofenac also produced a greater pain intensity reduction at rest and with activity.[44] There were no significant differences between the groups with respect to adverse events, and topical diclofenac was well tolerated.[44] Additional single-blinded or nonrandomized trials have assessed the topical diclofenac patch in acute injuries and have found it to be superior to placebo in relieving pain.[44]

Studies support the use of topical diclofenac in alleviating pain related to acute injuries, but its ability to improve muscle recovery and allow participants to return to activity more quickly remains to be appropriately evaluated. Topical diclofenac, because of its low systemic bioavailability, may be beneficial in those patients who are at risk for gastrointestinal or cardiovascular toxicity from oral NSAIDs.

Acetaminophen

Acetaminophen (Tylenol) was initially used in 1893 but did not gain wide acceptance until 1949.[14] Acetaminophen is the active metabolite of phenacetin, which was widely used until the 1980s when it was withdrawn from the market due to its association with analgesic-abuse nephropathy and hemolytic anemia.[14] Acetaminophen, along with NSAIDs, has largely replaced aspirin as the analgesic of choice in children, adolescents, and young adults, because of aspirin's association with Reye syndrome. Acetaminophen is known to have analgesic and antipyretic activity similar to aspirin; however, acetaminophen has poor anti-inflammatory effects. At typical doses of 1000 mg, acetaminophen has been shown in whole blood assays of healthy volunteers to inhibit only approximately 50% of COX-1 and COX-2 enzymes.[14] Acetaminophen has good bioavailability and is evenly distributed throughout most body fluids.[14] Protein binding of acetaminophen is variable, and it undergoes extensive hepatic metabolism with glucuronidation and sulfation to form inactive metabolites that are

excreted by the kidneys.[14] A small percentage (about 5%–15%) of acetaminophen is metabolized to *N*-acetyl-*p*-benzoquinoneimine (NAPQI), which normally reacts with glutathione sulfhydryl groups, is further metabolized, and then excreted.[45] When excessive amounts of acetaminophen are consumed, conjugation pathways become saturated and larger amounts of acetaminophen are converted to NAPQI.[14,45] With the shift to NAPQI, glutathione stores become depleted and the excessive NAPQI can lead to hepatotoxicity.[14,45]

Acetaminophen has mild to moderate analgesic properties as well as antipyretic activity. Acetaminophen has been used for a wide variety of indications, including fever and pain associated with many different conditions.[45] Contributing to acetaminophen's widespread use is its easy tolerability. Unlike NSAIDs, acetaminophen does not affect platelet function or uric acid levels, nor is it associated with significant gastrointestinal toxicity.[45] Acetaminophen is felt to be safe in patients with peptic ulcer disease and aspirin hypersensitivity, but is not a reasonable alternative to NSAIDs in patients with inflammatory conditions such as rheumatoid arthritis.[14] Side effects that have been reported, albeit infrequently, include rash, hypersensitivity reactions, blood dyscrasias, and renal toxicity.[45]

The most serious adverse event that may occur with acetaminophen is the risk for hepatotoxicity that occurs with overdose. The maximum adult dose of acetaminophen is 4000 mg per day and for those with chronic alcohol use, 2000 mg daily (**Table 5**).[14] Because of the vast number of preparations that contain acetaminophen, including prescription and OTC, accidental overdose can occur due to consumption of multiple products (ie, prescription analgesic agents and OTC cough and cold preparations). Whether accidental or intentional, acetaminophen overdose is a medical emergency.[14] Overdose can occur with single doses of 10 to 15 g, and doses of 20 to 25 g can be lethal.[14] Acetaminophen toxicity is divided into 4 stages. The first stage can occur within several hours of acute ingestion, is typically associated with nausea, vomiting, and stomach pain, and may resolve within 24 hours.[14,45] The second stage can start approximately 12 to 36 hours after acute ingestion, and is significant for right upper quadrant pain and elevated liver enzymes.[45] Stage 3 occurs 72 to 96 hours after ingestion of toxic doses, and hepatomegaly, jaundice, and coagulopathy may be

Table 5
Acetaminophen formulations and dosing

Formulation	Regular: 80 mg, 160 mg, 325 mg Extra strength: 500 mg Extended release: 650 mg Liquid: 80 mg/0.8 mg, 160 mg/5 mL, 500 mg/15 mL Rectal suppository: 80 mg, 120 mg, 325 mg, 650 mg
Dosage (adult and adolescent)	325–650 mg every 4–6 h as needed 1000 mg 3–4 times daily Not to exceed 4 g/d
Comments	80 mg and 160 mg available in chewable, oral disintegrating, and meltaways Shake suspension well before dispensing Avoid chronic use in hepatic impairment Chewable tablets may contain phenylalanine Avoid or limit alcohol to <3 drinks per day Avoid other products with acetaminophen

Data from Ref.[19]

present.[14,45] Liver enzyme levels peak during this time period and renal failure can be present. The onset of encephalopathy or worsening coagulopathy after this time period indicates a poor prognosis.[14] Stage 4 is the recovery period for those who make it past stage 3.[45] Acetaminophen overdose is best managed when early diagnosis and treatment can occur. It has been estimated that about 10% of those who do not receive proper treatment will develop severe hepatic impairment, and 10% to 20% of those may eventually die from liver failure.[14,45]

Several studies have evaluated acetaminophen and compared it with an NSAID for treating pain. A study by Dalton and Schweinle[46] compared acetaminophen extended-release to ibuprofen in 260 patients who presented with grade I or II lateral ankle sprains. At the end of the study, acetaminophen was found to be not inferior to ibuprofen; 78% to 80% of patients had resumed normal activities, and mean time to resumption was approximately 4 days in both groups.[46] A study by Woo and colleagues[47] recruited 300 patients who presented to an emergency room with an isolated painful limb injury. Patients were randomized to a 3-day course of acetaminophen, indomethacin, diclofenac, or acetaminophen and diclofenac. Pain reduction was seen in all treatment arms, with score reductions not found to be clinically or statistically significant among the 4 groups over the course of the 3 days.[47] The combination therapy group had the greatest reduction in pain scores at each time point but also produced more side effects, including abdominal pain.[47] Although the literature is not as extensive as for NSAIDs regarding the use of acetaminophen for treating musculoskeletal injuries, there is evidence to support its use.

TOPICAL NONPRESCRIPTION ANALGESICS

Nonprescription, or OTC, analgesic agents and external counterirritants are widely used in the United States, with more than $2 billion spent on them each year.[48] Due to their easy access without a prescription, OTC topical analgesics are often first used in treating acute injuries before scheduling a visit to the physician. Topical analgesics can have one of several different properties; those with counterirritant effects are indicated for the acute treatment of minor aches and pains. Counterirritants exert their effect by producing a less intense pain than the pain the individual is experiencing.[48] The perception of another sensation distracts the person from the original pain produced by the injury. Counterirritants can fall into 1 of 4 categories based on their mechanism: (1) act as rubefacients, (2) production of a cooling sensation, (3) producing vasodilation, and (4) causing irritation without rubefaction.[48] A classification of topical analgesics with counterirritant properties is outlined in **Table 6**. The FDA has approved these agents for use in treating minor aches and pain for both adults and children 2 years or older.[48] Counterirritants from different categories are often combined in various preparations to enhance the efficacy of the product.

Methyl Salicylate

Methyl salicylate is a commonly used rubefacient that is available naturally in wintergreen oil, or it can be produced by esterification of salicylic acid with methyl alcohol.[48] Methyl salicylate is thought to exert its effect by producing a local vasodilation, and the counterirritant effect results from the local increase in skin temperature.[48] Most of the effects of methyl salicylate are locally mediated; however, systemic absorption can increase with the use of multiple applications, and use with local application of heat and occlusive dressings.[48] The most common adverse effects are skin irritation and rash, but more severe skin reactions along with systemic toxicity can occur.[48] The use of heating pads should be avoided while using topical methyl salicylate because

Table 6
Classification of topical analgesics with counterirritant properties[48]

Group Classification	Mechanism	Counterirritant
I	Rubefacients	Methyl salicylate Turpentine oil Ammonia water
II	Cooling sensation	Camphor Menthol
III	Vasodilation	Histamine dihydrochloride Methyl nicotinate
IV	Irritation without rubefaction	Capsaicin Capsicum oleoresin[a]

[a] Capsaicin is the major ingredient in capsicum oleoresin. (*Data from* Wright E. Musculoskeletal injuries and disorders. In: Berardi R, Ferreri S, Hume A, et al, editors. Handbook of nonprescription drugs, an interactive approach to self-care. 16th edition. Washington, DC: American Pharmacists Association; 2009. p. 95–113).

tissue and muscle necrosis along with interstitial nephritis have been reported when topical methyl salicylate and menthol were used.[49] Methyl salicylate should be avoided in children and in individuals with aspirin sensitivity and asthma, due to the risk for systemic absorption.[48] Drug interactions with warfarin have been reported with typical and high-dose topical methyl salicylate, resulting in an elevation of the prothrombin time/international normalized ratio.[50,51]

Camphor

Most camphor is synthetically produced and exerts a counterirritant effect via a cooling sensation. Camphor stimulates skin nerve endings producing mild pain, which allows for a masking of the deeper-seated pain.[48] The major toxicity associated with camphor is tonic-clonic seizures. The risk for toxicity correlates with the amount and extent of the camphor ingested.[48] In addition to seizures, high doses have also been associated with nausea, vomiting, dizziness, delirium, coma, and death.[48] Concentrations of camphor oil at 20% and as little as 5 mL can be lethal when ingested by children.[48] As a result, in 1982 the FDA ruled that camphorated oil products could no longer be produced and products containing camphor must have concentrations less than 11% to be considered safe for nonprescription use.[52] Unfortunately, pediatric cases of toxicity from acute ingestions have continued to be reported with OTC preparations containing camphor.[48,52,53]

Menthol

Menthol, prepared synthetically or derived from peppermint oil, is another counterirritant when used at concentrations greater than 1.25%.[48] Menthol exerts its cooling effect by activating the transient receptor potential, TRPM8, in sensory neurons.[54] Menthol has also been associated with an increase in local blood flow at the application site, resulting in a warm sensation.[54] Menthol has been associated with a low incidence of hypersensitivity reactions including itching, erythema, and skin lesions, and postmarketing data indicate minimal toxicity.[54]

Capsaicin

Capsaicin, which is derived from hot chili peppers, produces an analgesic effect due to its direct irritant properties. Topical application of capsaicin produces a warm sensation locally due to activation of the TRP vanilloid (TRPV1); this effect decreases

with repeated administration due to tachyphylaxis.[55,56] Capsaicin depletes substance P (neurotransmitter for pain communication) from unmyelinated type C sensory neurons, which can produce an initial burning or itching sensation.[57] Blockade of further synthesis of substance P with repeated application leads to persistent desensitization.[57] The burning sensation diminishes with repeated use, but can lead to an increase in nonadherence and discontinuation of its use. Topical capsaicin has been recommended for use in osteoarthritis, and pain relief is usually seen within several weeks. Capsaicin is applied routinely 3 to 4 times daily to sustain its effect. Gloves should be used to minimize contact with mucous membranes.[48] As with other topical analgesics, capsaicin should not be applied to open wounds and should be discontinued if skin breakdown occurs.[48] Capsaicin has not been studied in acute sports-related injuries, and given that its analgesic effects may not be seen for several weeks, may make it less ideal for treatment.

Others

Other counterirritants not widely used include turpentine oil, histamine dihydrochloride, and ammonia water.[48] The efficacy of these agents is difficult to evaluate, because they are often used in combination with other counterirritant agents. Little data exist to support the use of eucalyptus oil and trolamine salicylate; however, trolamine salicylate continues to be available in a variety of topical analgesics. Trolamine salicylate is not a counterirritant and has been shown to be systemically absorbed.[48] In general, for trolamine salicylate 10% to 15%, is applied to the skin 3 to 4 times daily.[48] Contraindications, precautions, and drug interactions are similar to those of salicylates. Trolamine may be beneficial for those who are unable to tolerate other counterirritants or find them unacceptable.

Counterirritants are available in a wide variety of single and combination products as nonprescription analgesic agents (**Table 7**). Counterirritants are indicated for the treatment of mild aches and pains related to acute injury, and provide a useful option for self-treatment. General guidelines for use of topical counterirritant agents are outlined in **Box 1**.

USE AND ABUSE OF ANALGESICS

OTC medications are widely available and used in the United States. It is not uncommon for individuals to self treat for a wide variety of ailments, including acute musculoskeletal injuries. It has been estimated that 30% of adults have used one or more OTC medications within the past 2 days.[59] Children and adolescents are also consumers of OTC medications for cough and cold, headache, fever, menstrual, and joint and muscle pain. Chambers and colleagues,[59] administered a questionnaire to 651 junior high school students in Nova Scotia to evaluate the use of OTC medications, indications, and self-administration. Of those who used an OTC medication, 88% reported using it for muscle, joint, and back pain; acetaminophen was the most common medication used for each type of pain assessed.[59] Self-administration was common, with 58% to 76% reporting taking medication within the past 3 months without consulting any knowledgeable professional.[59]

With increasing self-administration and easily accessibility, factors that influence consumption of OTC medications have been evaluated. Van den Bulck and colleagues[60] evaluated the association between watching television and analgesic use in 2545 Belgian students (aged 13–16 years). Using a questionnaire, the investigators found that the use of analgesics differed among school years and between gender. A significant correlation was found between regular OTC analgesic use (at

Table 7
Topical analgesic agents

Preparation	Product	Ingredients
Menthol preparations	ActivOn Topical Analgesic Ultra Strength Joint and Muscle	Menthol 4.127%
	Icy Hot Extra Strength Medicated Patch	Menthol 5%
	Ben Gay Ultra Strength Pain Relieving Patch	Menthol 5%
	Absorbine Jr. Pain Relieving Liquid	Menthol 1.27%
	Aspercreme Heat Pain Relieving Gel	Menthol 10%
	Flexall Maximum Strength Relieving Gel	Menthol 16%
Camphor preparations	JointFlex Arthritis Pain Relieving Cream	Camphor 3.1%
Capsaicin preparations	Capzasin Arthritis Pain Relief No Mess Applicator	Capsaicin 0.15%
	Zostrix Arthritis Pain Relief Cream	Capsaicin 0.025%
	Zostrix HP Arthritis Pain Relief Cream	Capsaicin 0.075%
	WellPatch Natural Capsaicin Pain Relief Patch	Capsaicin 0.025%
Trolamine preparations	Aspercreme Analgesic Creme Rub	Trolamine 10%
	Mobisyl Maximal Strength Arthritis Pain Relief Creme	Trolamine 10%
	Sportscreme Deep Penetrating Pain Relieving Rub	Trolamine 10%
Combination preparations	Tiger Muscle Rub	Methyl salicylate 15% Menthol 5% Camphor 3%
	ActivOn Topical Analgesic Ultra Strength Backache	Histamine dihydrochloride 0.025% Menthol 4.127% Camphor 3.15%
	Salonpas Pain Patch	Camphor 1.12% Menthol 5.7% Methyl salicylate 6.3%
	Icy Hot Extra Strength Pain Relieving Chill Stick	Methyl salicylate 30% Menthol 10%
	Icy Hot Extra Strength Relieving Balm	Methyl salicylate 29% Menthol 7.6%
	Heet Pain Relieving Formula	Camphor 3.6% Methyl salicylate 18% Oleoresin capsicum 0.25%
	Freeze It Advanced Therapy Pain Relief, Roll On	Camphor 0.2% Menthol 3.5%

Data from Ref.[58]

least monthly) and viewing of television (odds ratio [OR] 1.16, 95% CI: 1.08–1.24).[60] Playing video games and Internet use was not significantly associated with analgesic use. The authors note that this study did not evaluate the extent to which adolescents were exposed to advertisements during television viewing.[60]

Self-administration of medications by children and adolescents can be influenced by multiple factors and is potentially dangerous. Huott and Storrow[61] surveyed 203 adolescents aged 13 to 18 years who presented to an emergency room or acute care clinic. The adolescents completed a 1-page survey assessing their knowledge of OTC medication toxicity. An informal survey of the investigators' colleagues and standard texts served as the reference point regarding medication toxicity.[61] Survey

Box 1
General guidelines for the use of topical analgesics

- Apply to affected areas of intact skin 3 to 4 times daily
- Massage or rub gently into the affected area
- Wash thoroughly with soap and water after application
- For patch application, clean and dry the affected areas and remove film before application
- Consider using gloves, especially for capsaicin application
- Capsaicin is contraindicated for those younger than 18 years
- Follow directions for each product carefully

results of the adolescents indicated that 63% considered aspirin, 57% acetaminophen, 24% iron, 22% camphor, and 17% to 21% methyl salicylate to be nonlethal, which was contradictory to the faculty's viewpoint.[61] The results of this study emphasize that education regarding the toxicity of OTC medications needs further emphasis.

While analgesic use is common among adolescents in general, the pattern of their use among student athletes in particular has not been clearly elucidated. Many student athletes experience muscle aches and pains as well as sports-related injuries, and may self-medicate with OTC analgesic agents including NSAIDs. Evidence indicates that many adolescents are unaware of the potential toxicity or risk for side effects associated with nonprescription analgesic medications. Warner and colleagues[62] distributed a self-administered questionnaire to 604 high school football athletes to compare users with nonusers of NSAIDs and discern differences in attitudes regarding daily use of NSAIDs. The study found that 75% had used NSAIDs in the past 3 months.[62] Of this cohort, 15% considered themselves daily users of NSAIDs.[62] After controlling for confounding variables, those who perceived that NSAIDs enhanced performance (adjusted odds ratio [AOR] 2.4; 95% CI 1.4–4.1), those who used prophylactic NSAIDs (AOR 2.5; 95% CI 1.5–4.3), and those who self-administered NSAIDs (AOR 2.2; 95% CI 1.01–4.9), were more likely to take NSAIDs on a daily basis.[62]

Often in athletes, student as well as elite, studies focus on medications of abuse rather than common prescription and nonprescription medications. Alaranta and colleagues[63] used a questionnaire to determine the frequency of prescribed medications in a group of elite athletes. In 2002, 446 athletes, supported by the National Olympic Committee, completed the survey and were matched to 1503 controls obtained from a population-based study done by the National Public Health Institute.[63] Among athletes, within the previous 7 days 34.5% were using a prescription medication compared with approximately 25% of the controls.[63] NSAIDs were among the most frequently prescribed medications (8.1%) in athletes, with an AOR of 3.63 (95% CI: 2.25–5.84) for use within the past 7 days.[63] Adverse events were reported in 20% of NSAID users.[63]

SUMMARY

The idea of ''no pain, no gain'' is a common misperception that should be dispelled. Muscle soreness can be expected with strenuous activity or due to an unaccustomed activity, but significant pain is the body's response that rest should occur to allow for healing.[6] Too often, athletes do not take the time off from training or competition to allow for adequate healing.[64] By using analgesics, in particular NSAIDs, pain may subside but further damage can result from continued exercise. Also, NSAIDs, via their

inhibition of prostaglandins, may impede the healing process and muscle regeneration after an acute injury. While these agents are relatively safe they are not without side effects, and caution is warranted. There is only limited evidence (albeit it conflicting) in DOMS that NSAIDs can provide a benefit as prophylactic therapy.

Overall, analgesic agents, including NSAIDs, acetaminophen, and topical OTC agents, can effectively relieve pain associated with acute or chronic musculoskeletal injury. Data regarding the ability of NSAIDs to improve muscle recovery and allow a quicker return to activity remain controversial. This area of focus has not been adequately studied with acetaminophen and topical OTC analgesics. When considering an analgesic for alleviating pain, the lowest dose for the shortest time interval should be used. Risk for side effects should be considered and compared with the benefits of the medication. Long-term use for symptoms of sport-related injuries should be avoided, especially with NSAIDs, due to their side effect profile and concern for their impeding the healing process. Data do not adequately support the use of prophylactic NSAIDs prior to sporting events, and should be avoided.

ACKNOWLEDGMENTS

The authors thank Kim Douglas and Amy Esman, Kalamazoo Center for Medical Studies, for assistance in the preparation of this article.

REFERENCES

1. Almekinders L. Anti-inflammatory treatment of muscular injuries in sport, an update of recent studies. Sports Med 1999;28(6):383–8.
2. Garrett WE. Muscle strain injuries: clinical and basic aspects. Med Sci Sports Exerc 1990;22:436–43.
3. Mehallo C, Drezner J, Bytomski J. Practical management: nonsteroidal anti-inflammatory drug (NSAID) use in athletic injuries. Clin J Sport Med 2006;16: 170–4.
4. Micheli L. Common painful sports injuries: assessment and treatment. Clin J Pain 1989;5(Suppl 2):S51–60.
5. Howatson G, van Someren K. The prevention and treatment of exercise-induced muscle damage. Sports Med 2008;38(6):483–503.
6. Smith B, Collina S. Pain medications in the locker room: to dispense or not. Curr Sports Med Rep 2007;6:367–70.
7. Almekinders LC, Gilbert JA. Healing of experimental muscle strains and the effects of non-steroidal anti-inflammatory medication. Am J Sports Med 1986; 14:303–8.
8. Crisco JJ, Jokl P, Heinen GT, et al. A muscle contusion injury model: biomechanics, physiology and histology. Am J Sports Med 1994;22:702–10.
9. Tidball JG. Inflammatory cell response to acute muscle injury. Med Sci Sports Exerc 1995;27:1022–32.
10. Kuipers H. Exercise-induced muscle damage. Int J Sports Med 1994;15:132–5.
11. Jarvinen TA, Jarvinen TL, Kaariainen M, et al. Muscle injuries biology and treatment. Am J Sports Med 2005;33:745–64.
12. Maroon J, Bost J, Borden M, et al. Natural anti-inflammatory agents for pain relief in athletes. Neurosurg Focus 2006;21(4):E11.
13. Herndon C, Hutchinson R, Berdine H, et al. Management of chronic nonmalignant pain with nonsteroidal anti-inflammatory drugs. Pharmacotherapy 2008;28(6): 788–805.

14. Burke A, Smyth E, FitzGerald G. Analgesic-antipyretic and antiinflammatory agents; pharmacotherapy of gout. In: Brunton L, Lazo J, Parker K, editors. Goodman and Gilman's, the pharmacological basis of therapeutics. 11th edition. New York: McGraw-Hill; 2006. p. 671–715.
15. Vane J, Botting R. Mechanism of action of nonsteroidal anti-inflammatory drugs. Am J Med 1998;104(3A):2S–8S.
16. Furst Daniel E, Ulrich Robert W, Varkey-Altamirano C. Nonsteroidal anti-inflammatory drugs, disease-modifying antirheumatic drugs, nonopioid analgesics, drugs used in gout. In: Bertram GK, Susan BM, Anthony JT, editors. Basic & clinical pharmacology. 11th edition. Chapter 36. Available at: http://0-www.accesspharmacy.com.libcat.ferris.edu/content.aspx?aID=4519955. Accessed February 5, 2010.
17. Smyth Emer M, FitzGerald Garret A. The eicosanoids: prostaglandins, thromboxanes, leukotrienes, related compounds. In: Bertram GK, Susan BM, Anthony JT, editors. Basic & clinical pharmacology. 11th edition. Chapter 18. Available at: http://0-www.accesspharmacy.com.libcat.ferris.edu/content.aspx?aID=4518588. Accessed February 5, 2010.
18. Vane J, Botting R. The mechanism of action of aspirin. Thromb Res 2003;110:255–8.
19. Lexi-Comp, Inc (Lexi-Drugs®). Lexi-Comp. Accessed December 21, 2009.
20. Natural medicines comprehensive database [database on the Internet]. Stockton (CA): Therapeutic Research Faculty; c1995–2009. Antiplatelet; [about 14 pages]. Available at: http://www.naturaldatabase.com/(S(wqklte55rbhkbvzskfpaim45))/nd/Search.aspx?cs=MHSLA%7ECP&s=ND&pt=9&Product=antiplatelet. Accessed December 21, 2009.
21. Kirchain W, Allen R. Drug-induced liver disease. In: DiPiro J, Talbert R, Yee G, et al, editors. Pharmacotherapy a pathophysiologic approach. 7th edition. New York: McGraw-Hill; 2008. p. 652.
22. Scheiman JM, Fendrick AM. Practical approaches to minimizing gastrointestinal and cardiovascular safety concerns with COX-2 inhibitors and NSAIDs. Arthritis Res Ther 2005;7(Suppl 4):S23–9.
23. Golstein JL, Eisen GM, Burke TA, et al. Dyspepsia tolerability from the patients' perspective: a comparison of celecoxib with diclofenac. Aliment Pharmacol Ther 2002;16:819–27.
24. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520–8.
25. Laine L. Nonsteroidal anti-inflammatory drug gastropathy. Gastrointest Endosc Clin N Am 1996;6:489–504.
26. Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. Ann Intern Med 1991;115:787–96.
27. Ekstrom P, Carling L, Wetterhuis S, et al. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous nonsteroidal anti-inflammatory drug therapy: a Nordic multicentre study. Scand J Gastroenterol 1996;31:753–8.
28. Hippisley-Cox J, Coupland C, Logan R. Risk of adverse gastrointestinal outcomes in patients taking cyclo-oxygenase-2 inhibitors or conventional non-steroidal anti-inflammatory drugs: population based nested case-control analysis. BMJ 2005;331:1310–6.

29. Bennett W, Turmelle Y, Shepherd R. Ibuprofen-induced liver injury in an adolescent athlete. Clin Pediatr 2009;48(1):84–6.
30. Rubenstein JH, Laine L. Systematic review: the hepatotoxicity of non-steroidal anti-inflammatory drugs. Aliment Pharmacol Ther 2004;20:373–80.
31. Rostom A, Goldkind L, Laine L. Nonsteroidal anti-inflammatory drugs and hepatic toxicity: a systematic review of randomized controlled trials in arthritis patients. Clin Gastroenterol Hepatol 2005;3:489–98.
32. Whelton A. Nephrotoxicity of nonsteroidal anti-inflammatory drugs: physiologic foundations and clinical implications. Am J Med 1999;106(Suppl 5B):S13–24.
33. Clive DM, Stoff JS. Renal syndromes associated with nonsteroidal anti-inflammatory drugs. N Engl J Med 1984;310:563–72.
34. Henrich WL. Nephrotoxicity of nonsteroidal anti-inflammatory agents. Am J Kidney Dis 1983;2:478–84.
35. Nakahura T, Griswold W, Lemire J, et al. Nonsteroidal anti-inflammatory drug use in adolescents. J Adolesc Health 1998;23:307–10.
36. Solomon S, McMurray J, Pfeffer M, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005; 352:1071–80.
37. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005; 352:1092–102.
38. McGettigan P, Henry D. Cardiovascular risk and inhibition of cyclooxygenase, a systematic review of the observational studies of selective and nonselective inhibitors of cyclooxygenase 2. JAMA 2006;296:1633–44.
39. COX-2 selective (includes Bextra, Celebrex, and Vioxx) and non-selective nonsteroidal anti-inflammatory drugs (NSAIDs). U.S. Food and Drug Administration, Drug Safety and Availability. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm103420.htm. Updated September 24, 2009. Accessed December 28, 2009.
40. Drug Facts & Comparisons [database on the Internet]. Facts & comparisons. Indianapolis (IN). 4.0; 2009. Nonsteroidal anti-inflammatory agents; [about 21 pages]. Available at: http://0-online.factsandcomparisons.com.libcat.ferris.edu/MonoDispaspx?id=570727&book=DFC. Accessed December 28, 2009.
41. Lanier A. Use of nonsteroidal anti-inflammatory drugs following exercise-induced muscle injury. Sports Med 2003;3:177–86.
42. Moore R, Tramer M, Carroll D, et al. Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. BMJ 1998;316:333–8.
43. Peterson B, Rovati S. Diclofenac epolamine (Flector®) patch, evidence for topical activity. Clin Drug Investig 2009;29(1):1–9.
44. Zacher J, Altman R, Bellamy N, et al. Topical diclofenac and its role in pain and inflammation: an evidence-based review. Curr Med Res Opin 2008;24(4): 925–50.
45. Drug Facts & Comparisons [database on the Internet]. Facts & comparisons. Indianapolis (IN). 4.0; 2009. Acetaminophen; [about 5 pages]. Available at: http://0-online.factsandcomparisons.com.libcat.ferris.edu/MonoDisp.aspx?monoID=fandc-hcp10022&quick=acetaminophen&search=acetaminophen&disease=. Accessed December 31, 2009.
46. Dalton J, Schweinle J. Randomized controlled noninferiority trial to compare extended release acetaminophen and ibuprofen for the treatment of ankle sprains. Ann Emerg Med 2006;48:615–23.

47. Woo W, Man S, Lam P, et al. Randomized double-blind trial comparing oral paracetamol and oral nonsteroidal anti-inflammatory drugs for treating pain after musculoskeletal injury. Ann Emerg Med 2005;46:352–61.
48. Wright E. Musculoskeletal injuries and disorders. In: Berardi R, Ferreri S, Hume A, et al, editors. Handbook of nonprescription drugs, an interactive approach to self-care. 16th edition. Washington, DC: American Pharmacists Association; 2009. p. 95–113.
49. Heng MC. Local necrosis and interstitial nephritis due to topical methyl salicylate and menthol. Cutis 1987;39(5):442–4.
50. Yip A, Chow W, Tai Y, et al. Adverse effect of local methylsalicylate ointment on warfarin anticoagulation: an unrecognized potential hazard. Postgrad Med J 1990;66(775):367–9.
51. Joss J, LeBlond R. Potentiation of warfarin anticoagulation associated with topical methyl salicylate. Ann Pharmacother 2000;34(6):729–33.
52. Love J, Sammon M, Smereck J. Are one or two dangerous? Camphor exposure in toddlers. J Emerg Med 2004;27(1):49–54.
53. Gouin S, Patel H. Unusual cause of seizure. Pediatr Emerg Care 1996;12(4): 298–300.
54. Patel T, Ishiuji Y, Yosipovitch G. Menthol: a refreshing look at this ancient compound. J Am Acad Dermatol 2007;57:873–8.
55. Vyklicky L, Novakova-Tousova K, Benedikt J, et al. Calcium-dependent desensitization of vanilloid receptor TRPV1: a mechanism possibly involved in analgesia induced by topical application of capsaicin. Physiol Res 2008;57(Suppl 3): S59–68.
56. Knotkova H, Pappagallo M, Szallasi A. Capsaicin (TRPV1 agonist) therapy for pain relief farewell or revival? Clin J Pain 2008;24:142–54.
57. Mason L, Moore A, Derry S, et al. Systematic review of topical capsaicin for the treatment of chronic pain. BMJ 2004;328:991.
58. Drugstore.com. Topical analgesics. Available at: http://www.drugstore.com/search/search_results.asp?N=0&Ntx=mode%2Bmatchallpartial&Ntk=All&srchtree=5&Ntt=topical+analgesics. Accessed January 10, 2010.
59. Chambers C, Reid G, McGrath P, et al. Self-administration of over-the-counter medication for pain among adolescents. Arch Pediatr Adolesc Med 1997;151: 449–55.
60. Van den Bulck J, Leemans L, Laekeman G. Television and adolescent use of over-the-counter analgesic agents. Ann Pharmacother 2005;39:58–62.
61. Huott M, Storrow A. A survey of adolescents' knowledge regarding toxicity of over-the-counter medications. Acad Emerg Med 1997;4:214–8.
62. Warner D, Schnepf G, Barrett M, et al. Prevalence, attitudes, and behaviors related to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in student athletes. J Adolesc Health 2002;30:150–3.
63. Alaranta A, Alaranta H, Heliovaara M, et al. Ample use of physician-prescribed medications in Finnish elite athletes. Int J Sports Med 2006;27(11):919–25.
64. Alaranta A, Alaranta H, Helenius I. Use of prescription drugs in athletes. Sports Med 2008;38(6):449–63.