Management of Chronic Nonmalignant Pain with Nonsteroidal Antiinflammatory Drugs

Joint Opinion Statement of the Ambulatory Care, Cardiology, and Pain and Palliative Care Practice and Research Networks of the American College of Clinical Pharmacy

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Chronic nonmalignant pain is a major burden on the health care system in the United States. Frequently, nonsteroidal antiinflammatory drugs (NSAIDs) are used to assist in the management of various chronic pain syndromes. Although evidence is accumulating on the potential toxicities associated with NSAIDs, clear recommendations are lacking to guide the appropriate use of these drugs. Equivocal data, especially with respect to cardiovascular risk, further confuse a clear treatment pathway when assessing pharmacotherapy. Originally, cyclooxygenase selectivity appeared to be a determining factor in choosing an agent because of the presumed lack of effect on the cardiovascular and gastrointestinal renal systems. This theory, however, was recently dispelled. To provide guidance on the selection of an NSAID for various chronic pain syndromes, members of the Ambulatory Care, Cardiology, and Pain and Palliative Care Practice and Research Networks of the American College of Clinical Pharmacy evaluated evidence-based use of NSAIDs for frequently encountered pain syndromes, with special focus on the adverse effects of this class of agents.

Key Words: nonsteroidal antiinflammatory drugs, NSAIDs, chronic nonmalignant pain, adverse effects.

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Chronic pain is the leading cause of adult disability in the United States. It is also the most common reason patients see a primary care clinician.[1] Pain, and particularly chronic pain, encompasses a complex array of sensory-discriminatory, motivational-affective, and cognitive-evaluative components.[2] Because of this complexity, both pharmacologic and nonpharmacologic approaches should be considered to treat pain. This joint opinion paper by the authorship panel representing the Ambulatory Care, Cardiology, and Pain and Palliative Care Practice and Research Networks of the American College of Clinical Pharmacy critically reviews the physiologic process of nociception, the pathophysiology of chronic pain, and the role nonsteroidal antiinflammatory drugs (NSAIDs) play in addressing the complex syndrome of chronic pain associated with osteoarthritis, rheumatoid arthritis, low back pain, fibromyalgia, and peripheral neuropathy. In addition, safety concerns associated with NSAID use in various patient subpopulations, including patients with comorbid health conditions, are outlined. Finally, consensus recommendations are provided on potential pain syndrome–specific alternatives for analgesia in patients at high risk for NSAID-induced adverse events.

Types of Pain

Chronic pain is defined as a persistent state of

pain in which the cause of the pain cannot be removed without analgesic pharmacotherapy and/or nonpharmacologic measures.[3] Chronic pain is often associated with long-term incurable or intractable medical conditions and may have psychologic and/or social factors. Chronic pain often lasts longer than physiologically necessary and may not be relieved by standard medical management. Chronic pain may result from a previous healed injury or from an ongoing cause such as arthritis, cancer, neuropathy, or an infectious process. With chronic pain, a normal lifestyle can be restricted or even impossible to maintain. The prevalence of chronic pain in the United States is difficult to accurately quantify; however, estimates as high as 20% of the total population have been quoted.[2]

Acute pain is a physiologic response to direct tissue injury and is often, but not always, associated with objective physical signs of autonomic nervous system activity. Chronic pain, in contrast to acute pain, rarely is accompanied by signs of sympathetic nervous system arousal. The lack of objective signs makes diagnostic confirmation difficult in those patients for whom an abnormality at imaging is disproportionate to or absent in the presence of ongoing pain. Chronic pain can be differentiated from acute pain in that acute pain signals a specific nociceptive event and is self-limited. Chronic pain may begin as acute pain, but it continues beyond the normal time expected for resolution of the problem or persists or recurs for other reasons.

Chronic inflammatory pain is associated with an ongoing response to injury or chronic systemic disease (e.g., rheumatoid arthritis) that may be characterized by redness, heat, swelling, and/or loss of function. The chronic inflammatory response is no longer a homeostatic mechanism to initiate the healing process from infection or injury and may decrease individual functional activity and subsequent quality of life.

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Physiology of Nociception

Arachidonic acid is broken down by prostaglandin G and H synthase (cyclooxygenase [COX]) enzymes and lipoxygenases to form a number of active products (Figure 1). The COX enzymes are dichotomous proteins, possessing both COX and hydroperoxidase activities and catalyzing the biotransformation of arachidonic acid into the prostaglandin endoperoxide intermediates: prostaglandin G_2 and prostaglandin H_2. These are, in turn, acted on by isomerases and synthases to form the prostaglandins and thromboxane A_2. The NSAIDs, which include both nonselective and selective inhibitors of COX-2, are frequently used for chronic pain management (Figure 2, Table 1).[3,4] Pain relief and decreased inflammation result from suppression of the COX function of prostaglandin H synthase and the consequent formation of prostaglandin E_2 and prostaglandin I_2 (prostacyclin).

Numerous classes of NSAIDs exist, representing a wide variety of pharmacokinetic and pharmacodynamic properties. Primary classes include salicylates, nonacetylated salicylates, propionic acids, fenamates (anthranilic acids), acetic acids, naphthylalkanones, oxicams, and COX-2 inhibitors (Table 1). Although most of the agents

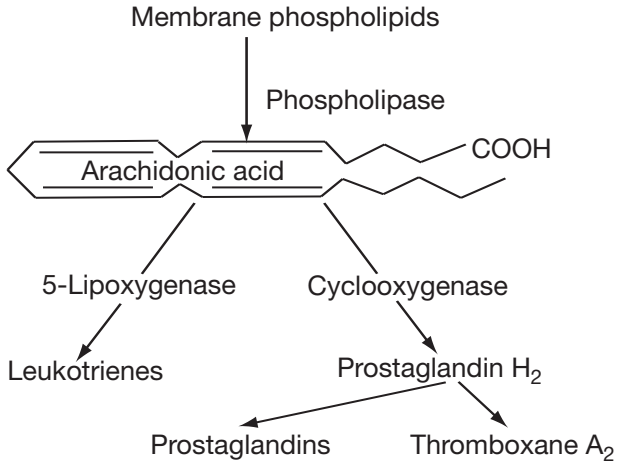

Figure 1. The phospholipid pathway.

ultimately affect similar inflammatory and nociceptive pathways, the chemistry, pharmacokinetic, and pharmacodynamic differences among classes allow clinicians flexibility when selecting patient-centered initial therapy.

Nonsteroidal Antiinflammatory Drug Therapy for Various Chronic Pain Syndromes

Osteoarthritis and Rheumatoid Arthritis

Osteoarthritis is a disease of the synovial joints characterized by the deterioration of cartilage and the reformation of bone. The disease typically affects the joints of the hands, knees, hips, neck, and lumber spine. Pain and subsequent functional loss are the primary reasons that patients seek medical care for osteoarthritis. Common treatments include nonpharmacologic therapy (e.g., weight reduction, physical therapy), pharmacotherapy (e.g., acetaminophen, NSAIDs, injection therapies), and, in some cases, surgery (e.g., joint replacement).[5, 6]

The European League Against Rheumatism (EULAR) Osteoarthritis Task Force published separate recommendations for the management of knee osteoarthritis and hip osteoarthritis.[7, 8] It should be noted that therapy for osteoarthritis of the hip is similar to treatment of osteoarthritis of the knee, except for a few minor differences. Topical NSAIDs have not been studied in patients with hip osteoarthritis, and their efficacy is questionable because of the depth of that joint. The EULAR recommendations for knee osteoarthritis (2000) and the American College of Rheumatology recommendations for hip and knee osteoarthritis (2000) both stated that NSAIDs should be reserved for patients unresponsive to acetaminophen.[7–9] More recently, EULAR released an updated practice recommendation that differs little from the previous reports. When specifically addressing osteoarthritis of the hand, EULAR acknowledges the adverse-effect profiles of NSAIDs in general and continues to support acetaminophen and topical NSAIDs before systemic NSAID therapy. In addition, the EULAR consensus panel continues to recommend that NSAIDs be considered at the lowest doses and shortest durations feasible.[10]

Further data supporting acetaminophen as the initial pharmacologic treatment over NSAIDs for both knee and hip osteoarthritis are derived from the Cochrane database. A Cochane review of six randomized controlled trials compared the safety and efficacy of acetaminophen and NSAIDs administered for a mean duration of 5.8 wks in 1689 patients with osteoarthritis.[11] Acetaminophen

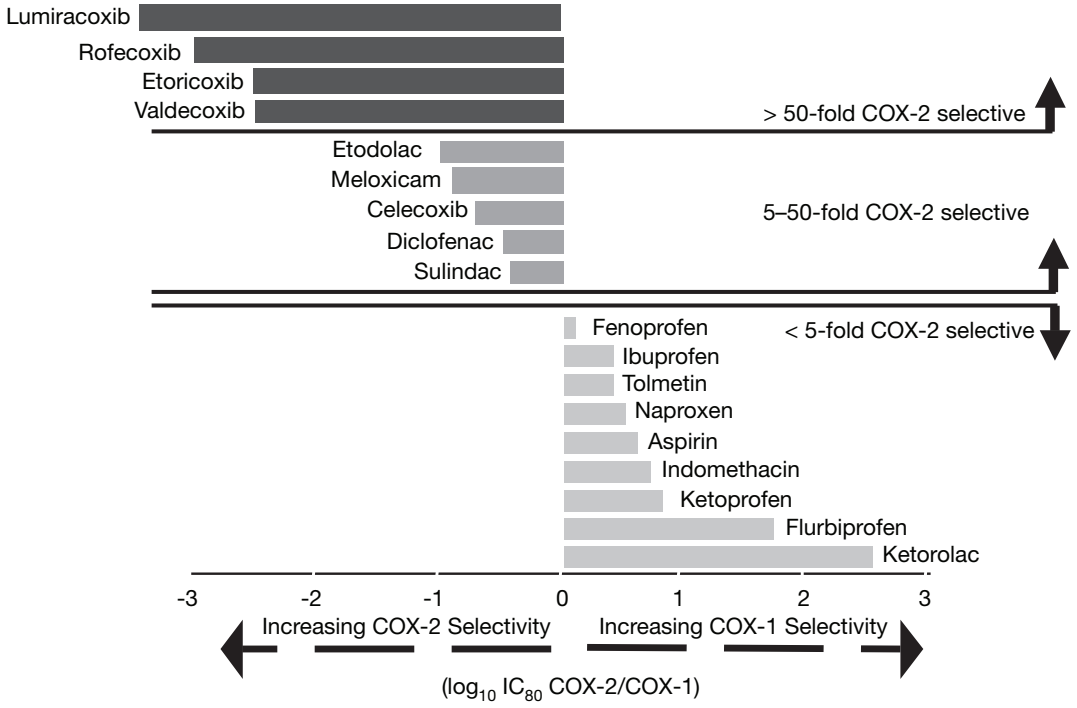

Figure 2. In vitro selectivity for cyclooxygenase (COX) enzymes of various nonsteroidal antiinflammatory drugs. IC_{80} = drug concentration that inhibits 80% of the COX enzyme. (Adapted from reference 4.)

and NSAIDs produced equal functional improvement, but NSAIDs were slightly better in pain reduction and physician global assessment. Acetaminophen use was associated with fewer withdrawals and fewer gastrointestinal adverse events.

Rheumatoid arthritis is an inflammatory condition characterized by a symmetric pattern of inflammation of the joint-lining membrane. In rheumatoid arthritis, the body's immune system attacks bone, cartilage, and sometimes internal organs, leading to swelling, pain, stiffness, and possible loss of function. Treatments include physical therapy, exercise, disease-modifying antirheumatic drugs (DMARDs), NSAIDs for symptom control, and surgical intervention.[5] Chronic low-grade inflammation was recognized recently as an important risk factor for the development of atherosclerosis and, more recently, for the development of heart failure. Therefore, it appears patients with rheumatoid arthritis are at increased risk for morbidity and mortality from ischemic cardiovascular events and heart failure.[12, 13]

Practice guidelines from both the American College of Rheumatology and EULAR focus on early detection of rheumatoid arthritis, joint protection, rapid initiation of a DMARD, and palliation of painful symptoms.[6, 14] Both organizations' guidelines address the lack of disease-modifying outcomes associated with NSAID therapy in patients with rheumatoid arthritis. The American College of Rheumatology recommends NSAIDs initially to reduce pain and inflammation, as well as to preserve joint function. These agents may serve useful for symptomatic management of rheumatoid arthritis in the interim of DMARD initiation or time to DMARD benefit. Consideration of the risk profiles of these agents should be noted in this patient population, specifically gastroduodenal and cardiovascular risks. These risks, as they pertain to patients with rheumatoid arthritis, are addressed within their respective sections of this article.

Low Back Pain

Low back pain may be categorized based on the duration of symptoms from the time of onset, as well as the location and characterization of pain symptoms. Acute low back pain usually lasts for less than 6 weeks, does not radiate beyond the knees, and improves without treatment in over 90% of individuals.[15, 16] Chronic low back pain has symptoms that persist beyond 6 weeks and may radiate down one or both legs below the knees; further evaluation of pain and imaging studies are warranted. Chronic low back pain is frequently complicated with radicular symptoms that may or may not be a result of sciatic nerve involvement.

The effectiveness of NSAIDs in treating low back pain is controversial, with considerable amount of conflicting evidence. In 1987, the Quebec Task Force on Special Disorders reported that the efficacy of most interventions, including NSAIDs, in the treatment of low back pain was not well established by well-designed, randomized clinical trials. More than 20 years later, still no studies, to our knowledge, have shown that NSAIDs produce durable improvements in disability, and the efficacy of treating low back pain beyond 4 weeks with NSAIDs has not been established by sufficient randomized controlled trials.[17, 18]

One small, double-blind, crossover study in 37 patients compared naproxen sodium 275 mg twice/day, diflunisal 500 mg twice/day, and placebo in the treatment of chronic low back pain.[19] All treatments were given for 14 days, and patients were assessed with respect to global pain, night pain, pain on movement, and pain on standing. Naproxen relieved global pain better than placebo and, depending on the method of measurement, was superior in relieving night pain and pain on movement. In studies comparing a COX-2 inhibitor (etoricoxib) with placebo for the treatment of chronic low back pain, the COX-2 inhibitor provided slightly greater improvement in pain score and function for a longer duration (4 and 12 wks, respectively).[17, 20] However, none of the NSAIDs have been shown to be effective in the long-term treatment of chronic low back pain.[21]

Fibromyalgia

Fibromyalgia is a chronic pain disorder characterized by widespread musculoskeletal pain and trigger-point tenderness.[22] Diagnostic criteria for fibromyalgia developed by the American College of Rheumatology include a history of widespread body pain, including axial skeletal pain, plus pain upon digital palpation in at least 11 of 18 tender point sites.[22] Since most of these patients also experience stiffness, sleep disturbance, and/or fatigue, fibromyalgia is considered a syndrome. The overall prevalence of fibromyalgia syndrome is approximately 2% in

Table 1. Comparison of Chemistry, Pharmacokinetic, and Pharmacodynamic Parameters Among Oral Nonsalicylated and Salicylated NSAIDs and a COX-2 Inhibitor[3]

Drug	Onset of Action (hrs)	Duration of Effect (hrs)	Bioavailability (%)	Time to C_{max} (hrs)	Protein Binding (%)	Metabolism
Nonsalicylated NSAIDs						
Diclofenac	1–4.5	12–24	100	~1–2	99	Hepatic
Fenoprofen	~72	4–6	80	~2	99	Hepatic
Flurbiprofen	~1–2	Variable	96	~2	99	Hepatic: CYP2C9
Ibuprofen	Analgesic: 0.5–1 Antiinflammatory: ≤ 7 days	4–6	85	~1–2	90–99	Hepatic: CYP2C9
Indomethacin	~0.5	4–6	100	2	99	Hepatic and enterohepatic recirculation
Ketoprofen	0.5	6	~90	IR: ~0.5–2 ER: ~6–7	> 99	Hepatic
Meclofenamate	< 1	4–6	~100	0.5–2	> 99	Hepatic
Mefenamic acid	2–4	≤ 6	NA	2–4	> 90	Hepatic
Nabumetone	~72	Variable	NA	2.5–4	> 99	Hepatic
Naproxen	Analgesic: 1 Antiinflammatory: 2 wks	Analgesic: ≤ 7 Antiinflammatory: ≤ 12	95	IR: ~1–2 ER: ~4	> 99	Hepatic
Oxaprozin	~0.5–4	Variable	95	3–5	> 99	Hepatic
Piroxicam	~1	Variable	NA	3–5	99	Hepatic and enterohepatic recirculation
Sulindac	Analgesic: ~1	~12–24	~90	~2 (fasting) 3–5 (with food)	90	Enterohepatic
Tolmetin	Analgesic: ~1–2 Antiinflammatory: several days–1 wk	Variable	NA	~0.5–1	99	Hepatic
Salicylated NSAIDs						
Aspirin	~0.5	Analgesic: ~4–6	50–75	1–2	75–90[a]	Hepatic[b]
Diflunisal	Analgesic: ~1	Analgesic: 8–12 Antiinflammatory: ≤ 12	NA	2–3	> 99	Hepatic[d]
Salsalate	NA	NA	NA	72–96	80–90	Hepatic[e]
Choline salicylate	~2	NA	NA	~2	80–90	Hepatic
Magnesium salicylate	NA	4–6	NA	1.5	50–90	Hepatic
COX-2 inhibitor						
Celecoxib	Analgesic: ~0.75–several months	~4–8	NA	3	97	Hepatic: CYP2C9

NSAID = nonsteroidal antiinflammatory drug; COX-2 = cyclooxygenase type 2; C_{max} = maximum concentration; CYP2C9 = cytochrome P450 subfamily IIC, polypeptide 9; IR = immediate release; ER = extended release; NA = not available.
[a]Concentration dependent: 90% for low concentration (< 100 µg/ml) and 75% for high concentration (> 400 µg/ml).
[b]Substrate of CYP2C8 and CYP2C9 (minor).
[c]2–3% (urine pH 5), > 80% (urine pH 6.5).
[d]Glucuronidation.
[e]Major metabolic product is salicylic acid.

the United States, with more women affected than men. Prevalence increases proportionate to age, with the highest prevalence (> 7%) found in women aged 60–79 years[23]; however, the syndrome may be experienced by younger adults as well.[24]

Table 1. (continued)

Elimination Half-Life (hrs)	Excretion (%)	Volume of Distribution
1–2	Urine: 65 Feces: 35	1.4 L/kg
2.5–3	Urine	0.11–0.33 L/kg
4.7–5.7	Urine	0.12 L/kg
2–4	Urine	0.14 L/kg
4.5	Urine: 60 Feces: 33	0.34–1.57 L/kg
IR: 2–4 ER: ~3–7.5	Urine and feces	23.3 L
1.3	Urine and feces	23.3 L
2	Urine: 50 Feces: ~20	1.06 L/kg
~24	Urine: 80 Feces: 9	24–82 L
12–17	Urine: 95	0.16 L/kg
~40–50	Urine: 65 Feces: 35	10–12.5 L
~50	Urine and feces	0.14 L/kg
Parent: ~8 Active metabolite: ~16	Urine: 50 Feces: 25	NA
Biphasic rapid: 1–2 Slow: ~5	Urine	0.098 L/kg
Parent: ~0.25–0.33 Salicylate: ~3–10	Variable[c]	10 L
8–12	Urine: ~90	7.53 L
7–8	Urine	0.15–2 L/kg
Low dose: ~2–3 High dose: ~30	Urine	NA
~2–3	Urine	0.17 L/kg
11	Urine: 27 Feces: 57	400 L

Treatment options for fibromyalgia syndrome include patient education, aerobic exercise, physical therapy, cognitive behavioral therapy, and drug therapy.[25] First-line considerations for pharmacologic treatment include the tricyclic antidepressants or cyclobenzaprine, a skeletal muscle relaxant that is structurally similar to the tricyclic antidepressants.[25, 26] Although amitriptyline by far has the most clinical data on efficacy concerning patients with fibromyalgia syndrome, the studies unfortunately are relatively small and equivocal in their results.[25, 27] Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, and tramadol may also be considered as second-line options for pain control.[25, 26]

The NSAIDs have not been shown to be superior to placebo in clinical trials and therefore are not recommended as a primary treatment option in patients with fibromyalgia syndrome.[28–32] However, they may be effective when used with other pharmacologic treatment, such as amitriptyline or cyclobenzaprine.[29, 30, 33] This may be due, in part, to the fact that patients with fibromyalgia syndrome often have concurrent inflammatory processes (e.g., osteoarthritis or rheumatoid arthritis) that are responsive to the analgesic and antiinflammatory effects of NSAIDs.[34] Proposed theories for the lack of efficacy of NSAIDs in patients with fibromyalgia syndrome include the fact that NSAIDs produce their analgesic effects through peripheral mechanisms, whereas the pain of fibromyalgia may be due to central nervous system disturbances.[28, 35] The American Pain Society does not recommend NSAIDs as monotherapy but states that benefit may be realized when used in combination with other drugs.[26]

Peripheral Neuropathy

Peripheral neuropathy is a general term that refers to a variety of chronic pain conditions that result from damage to peripheral nerves. The causes of peripheral neuropathy are many and can include metabolic disturbances (e.g., diabetes mellitus, uremia), toxins (e.g., alcohol, drugs, lead), and infections (e.g., human immunodeficiency virus, herpes zoster).[36] Clinical manifestations of peripheral neuropathy include hyperalgesia, allodynia, paresthesia, and dysesthesia and are typically described by patients as tingling, shooting, electric-like, or burning pain.[36] Effective pharmacologic treatments for pain from peripheral neuropathies include tricyclic antidepressants, selected anticonvulsants (e.g., gabapentin, pregabalin, carbamazepine), serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, the 5% lidocaine patch, tramadol, and opioids, with the efficacy of each treatment option varying with the etiology of the neuropathy.[37–41]

Although NSAIDs are used by patients and health care providers to treat neuropathic and mixed pain syndromes, very little data exist supporting their use for these conditions. To our knowledge, only one study, published in 1987, has examined NSAID utility in patients with neuropathic pain. This was a small clinical trial that reported statistically significant reductions in diabetes-related paresthesias in patients taking ibuprofen and sulindac compared with placebo.[42] The NSAIDs have exhibited efficacy in carpal tunnel syndrome and acute sciatica; however, there is a paucity of data to support their use in painful peripheral or central neuropathies.[43–46]

Adverse Events Associated with Nonsteroidal Antiinflammatory Drug Therapy

Cardiovascular Events

The role of prostaglandins in acute hemostasis is complex and involves the interaction of different tissues and prostanoids. Endothelial cells produce prostaglandin I_2, which possesses both antithrombotic and vasodilatory properties. Cyclooxygenase-2 is the primary isoform found in endothelial cells and therefore is mainly responsible for the local conversion of arachidonic acid to prostaglandin H_2.[47, 48] However, platelet production of thromboxane A_2, a potent inducer of platelet adhesion and aggregation, is mediated by COX-1.[48–50] The vasculature normally maintains a healthy balance between endothelial-derived prostaglandin I_2 and platelet-derived thromboxane A_2.[47, 48] Disruption of this delicate balance may result in deleterious alterations in hemostasis.

Cyclooxygenase selectivity may be one explanation for the varying risks of cardiotoxicity observed with antiinflammatory agents. Using the ratio of the drug concentrations that inhibit 80% of the COX-2 and COX-1 enzymes (IC_{80} COX-2:COX-1 ratio), the selectivity index can be calculated.[51, 52] A selectivity index ratio of more than 1 indicates the drug is more COX-2 selective, whereas a ratio less than 1 indicates that the drug is more COX-1 selective.[53] The traditional nonselective antiinflammatory agents have index ratios that range from 0.05–10.[52–55] The United States Food and Drug Administration (FDA)–approved COX-2 inhibitors have index ratios that range from 30–250.[51, 53]

Both COX-1 and COX-2 play a significant role in renal function and perfusion, as sodium retention and glomerular filtration are dependent on the presence of both isoforms.[56, 57] A recent meta-analysis measured the risks of selective COX-2 inhibition on a composite renal outcome consisting of renal dysfunction, peripheral edema, and hypertension. Rofecoxib was associated with an increased risk of peripheral edema (relative risk [RR] 1.43, 95% confidence interval [CI] 1.23–1.66), hypertension (RR 1.55, 95% CI 1.29–1.85), and renal dysfunction (RR 2.31, 95% CI 1.05–5.07), whereas celecoxib was associated with a lower risk of both renal dysfunction (RR 0.61, 95% CI 0.40–0.94) and hypertension (RR 0.83, 95% CI 0.71–0.97) as compared with controls.[58] Other studies have confirmed the negative effects of selective and nonselective prostaglandin inhibition on edema and blood pressure.[59–61]

Patient-specific characteristics of the sample population may contribute to the variation in cardiotoxicity observed with a given agent. The selective COX inhibitors have been studied in a wide variety of situations, including the treatment of arthritis, in conjunction with cardiac bypass, and in cancer prevention. Even within a perceived homogeneous group, there can be significant differences in cardiovascular complications. For example, osteoarthritis and rheumatoid arthritis may appear to be relatively inert disease states with regard to cardiovascular risk. However, several studies have confirmed that rheumatoid arthritis is associated with an increase in cardiovascular mortality.[62–64] Higher cardiovascular risk has not been observed in patients with osteoarthritis. Minor disturbances in the prostaglandin cascade may be overexaggerated in patients who have baseline cardiovascular risk factors.

The cardiotoxic effects of selective prostaglandin inhibition were first documented in the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial and the Celecoxib Long-term Arthritis Safety Study (CLASS).[65, 66] Since these publications, several additional meta-analyses and reviews have attempted to define the risks of selective COX inhibition. Several investigations observed increases in cardiovascular risk with both low-dose (≤ 25 mg/day) and high-dose (> 25 mg/day) rofecoxib.[67–70] Cardiovascular risks are recognized with high-dose (> 200 mg/day) celecoxib, whereas the cardiotoxic effects of low doses (≤ 200 mg/day) are less understood.[71, 72] These safety concerns appear early in therapy and are not delayed as once described.[72–75] Although the cardiotoxic effects were thought to be limited to myocardial infarctions, a recent analysis has discovered an increase in arrhythmias as well.[58]

The selectivity of COX inhibition seen with

NSAIDs helps to predict their cardiovascular risk profiles. Relatively selective NSAIDs, such as diclofenac and meloxicam, appear to be associated with more untoward cardiovascular effects than nonselective inhibitors such as naproxen. Observational and randomized trials have documented cardiovascular risks with diclofenac similar to those observed with the selective COX-2 inhibitors.[76–79] In contrast, data suggest that naproxen may possess a neutral cardiovascular profile and may perhaps even be cardioprotective.[72, 76, 80–82] The safety concerns with naproxen are possibly offset by its antiplatelet properties, which mirror aspirin with scheduled doses.[83] Ibuprofen, although studied less extensively than naproxen for risk of acute myocardial infarction, also appears to possess a somewhat limited risk profile when compared with diclofenac, especially in those with no major risk factors for cardiovascular disease.[84, 85]

Unfortunately, the patient populations most likely to be prescribed these drugs for pain relief are often the same populations with cardiovascular risk factors. It does not appear that the toxic effects of the selective inhibitors can be avoided by restricting their use to short durations. Selection of therapy must weigh cardiovascular risk as well as benefit, other risks of therapy, and costs.

The American Heart Association has recently released a scientific statement with stepwise recommendations for those with cardiovascular disease or risk factors for ischemic heart disease.[86] These authors use a stepwise approach to treating acute musculoskeletal pain for those select patients with either cardiovascular disease or risk factors for ischemic heart disease. The scientific statement recommends acetaminophen, aspirin, tramadol, and opioid analgesics as first-line therapy in these at-risk patients, followed by nonacetylated salicylates as a potential second-line option. Once these options have been exhausted, NSAIDs with the lowest specificity for the COX-2 isoenzyme are recommended. In addition, as dosage and duration appear to be confounding variables in cardiovascular risk with NSAIDs, the lowest effective dose should be chosen for the shortest duration of time. Currently, selective inhibition of the COX-2 isoenzyme is purported to effect a myriad of normal and reactive physiologic processes. As dosages change for the various NSAIDs, regardless of classification, changes in pharmacology may also be observed.[87] Unfortunately, little data exist to examine the potential cardiovascular risk associated the nonacetylated salicylates.

Despite an abundance of meta-analyses focusing on specific outcomes, specific NSAIDs, specific dosages, and specific durations of therapy, the American Heart Association bases its recommendations on the FDA Arthritis Advisory Committee and Drug Safety Risk Management Advisory Committee joint meeting convened April 6, 2005, and on three large meta-analyses discussed previously in this section.[71, 72, 88, 89] Based on the data from these meta-analyses, and other large studies presented within, naproxen and ibuprofen appear to be the safest with respect to cardiovascular risk, when specifically measuring cardiovascular events and mortality. Also, naproxen appears to convey a statistically significant protective outcome in terms of cardiovascular events (RR 0.64, 95% CI 0.49–0.83).[89] Although there appear to be cardiovascular risk profiles associated with higher COX-2:COX-1 selectivity indexes, a recently published meta-analysis of randomized controlled trials studying celecoxib did not support the theory of either a class effect or a dose-dependent increase in risk for those exposed to celecoxib.[90] Until all of the potential confounders in these various studies are realized, evaluating the true benefit:risk ratio of this particular selective NSAID will prove challenging.

Gastrointestinal Events

Gastrointestinal safety continues to be a high priority for patients and clinicians when choosing an NSAID treatment for pain. Indeed, the gastrointestinal harm induced by NSAIDs may be the most prevalent adverse event associated with any drug class. Because of the widespread use of these agents, the potential for a large number of adverse events is alarming. The NSAIDs are among the most frequently used class of drugs worldwide, with over-the-counter sales of $30 billion annually.[91] Table 2 lists the NSAIDS available in the United States and their relative association with gastrointestinal adverse events. These effects are generally dose dependent, although their true frequencies are difficult to determine.[92]

Gastrointestinal adverse events associated with NSAID use are reported to account for more than 100,000 hospitalizations and more than 15,000 deaths annually.[93] Noteworthy are the number of hospitalizations for patients taking long-term, low-dose aspirin who are admitted with upper gastrointestinal bleeding. This accounts for about 10–15% of the hospital admissions for

Table 2. Frequency of Gastrointestinal Events Associated with NSAIDs

Drug	Percentage of Patients							
	Overall Minor Gastrointestinal Events	Dyspepsia	Nausea or Vomiting	Abdominal Pain	Gastritis	Abdominal Bleed	Peptic Ulcer	Perforation
Acetic acids								
Diclofenac	≤ 20	3–9	3–9	3–9	—	1.6	1.6	< 2
Etodolac	3–9	10	3–9	1–3	—	< 1	< 1	< 1
Indomethacin	—	3–9	3–9	1–3	—	> 1	> 1	> 1
Ketorolac	7 (diarrhea)	12	12	13	—	0.4–4.6[a] 2.1–15.4[b]	0.4–4.6[a] 2.1–15.4[b]	0.4–4.6[a] 2.1–15.4[b]
Sulindac	—	3–9	3–9	10	—	< 1	< 1	< 1
Tometin	—	3–9	11	3–9	1–3	< 1	1–3	< 1
COX-2 inhibitor								
Celecoxib	—	8.8	3.5	4.1	1.9	< 0.1	1.5–5.9	< 0.1
Fenamate								
Meclofenamate	10–33 (diarrhea)	1–3	11	—	—	< 1	1–3	< 1
Naphthylalkanone								
Nabumetone	14 (diarrhea)	13	3–9	12	1–3	< 1	< 1	< 1
Oxicams								
Meloxicam (7.5 mg, 15 mg)	—	4.5, 4.5	3.9, 3.8	1.9, 2.6	< 1	< 1	< 1	< 1
Piroxicam	—	1–10	1–10	1–10	< 1	1–10	1–10	1–10
Propionic acids								
Fenoprofen	—	3–9	3–9	—	< 1	< 1	< 1	< 1
Flurbiprofen	—	1–9	1–9	1–9	1–3	1–3	—	—
Ibuprofen	4–16	≤ 9	≤ 9	≤ 9	—	< 1	< 1	< 1
Ketoprofen	—	11	3–9	3–9	—	< 1[c] > 2[d]	< 1[c] > 2[d]	< 1[c] > 2[d]
Naproxen	—	1–3	3–9	3–9	—	< 1	< 1	< 1
Oxaprozin	—	> 1	> 1	> 1	—	> 1	> 1	> 1
Salicylates								
Acetylated Aspirin	2–10[e] 10–30[f] 30–90[g]	—	—	—	—	—	—	—
Nonacetylated								
Choline salicylate	—	≤ 30	≤ 30	≤ 30	< 1	—	< 1	—
Choline magnesium trisalicylate	—	≤ 20	≤ 20	≤ 20	< 1	< 1	< 1	—
Diflunisal	—	3–9	3–9	3–9	—	1[c] 4[h]	1[c] 2–4[h]	1[c] 2–4[h]
Salsalate	—	≤ 30	≤ 30	≤ 30	< 1	—	<1	—

NSAID = nonsteroidal antiinflammatory drug; COX-2 = cyclooxygenase type 2.
[a]No history of peptic ulcer or bleed.
[b]With history of peptic ulcer or bleed.
[c]If treated for 3–6 mo.
[d]If treated for > 6 mo.
[e]Dose < 3.6 g/day.
[f]Dose ≥ 3.6 g/day.
[g]Preexisting gastrointestinal disease.
[h]If treated up to 1 yr.
Adapted from reference 92.

upper gastrointestinal bleeding. The economic cost of treating gastrointestinal adverse events associated with the use of NSAIDs is estimated to be $0.66–1.25 for every dollar spent on the cost of the NSAID.[94] Gastrointestinal adverse events are more likely to occur with long-term use and with higher doses of the NSAID.

Even though gastrointestinal toxicity remains a

clinically and economically important problem, reported U.S. data may need to be reevaluated. These data were derived from a rheumatoid arthritis patient population, which has a higher all-cause mortality rate than the overall population.[95] A recently published survey of the hospitals in the Spanish National Health System reported a frequency of 15.3 deaths/100,000 NSAID users.[95] These deaths occurred in 5% of all patients hospitalized with gastrointestinal complications secondary to NSAID use. Mortality rates were only 30% of those reported in the United States, and one third of the mortality occurred in patients taking low-dose aspirin. The differences may be accounted for by the fact that only 29% of NSAID users in the United States take proton pump inhibitor (PPI) therapy concurrently compared with greater than 50% of Spanish NSAID users.

When discussing gastrointestinal events, it is necessary to define the event and the location. Upper gastrointestinal adverse events manifest as dyspepsia, nausea, abdominal pain, gastric and duodenal mucosal erosions, and ulcers and ulcer complications. Most of the ulcer complications are ulcer bleeding events, with perforation and gastric outlet obstruction being rare. Often overlooked are lower gastrointestinal events related to the use of NSAIDs. In the Spanish study cited above,[95] the estimate for lower bowel gastrointestinal events was 14% of the total gastrointestinal complications, higher than in previously reported data.[96] Ulcers and strictures of the small or large bowel are responsible for blood loss associated with NSAIDs. The clinical relevance of lesions in the small bowel, however, remains to be determined. Other problems in the lower gut linked to the use of NSAIDs are gut inflammation, increase in gut permeability, ulceration, stricture, protein malabsorption, bleeding, and perforation.[97]

Dyspeptic symptoms include epigastric pain, bloating, nausea, and heartburn, which account for the most common reason for discontinuation of NSAID therapy. The exact mechanism of NSAID-related dyspepsia is unclear. However, alterations in gastric motility and reductions in prostaglandin synthesis affecting the integrity of the mucosa are implicated in the destructive pathways. Both selective and nonselective NSAIDs are associated with dyspepsia.[98]

Gastric or duodenal ulceration occurs in about 20% of NSAID users, and 40% of these individuals develop a serious complication.[65] Clinically significant ulcer complications include symptomatic ulcers, hemorrhagic ulcers, and ulcer perforations. Patients may present with a serious gastrointestinal adverse event, yet had no symptoms before the event occurred. Moreover, there appears to be no correlation between endoscopic findings for mucosal injury and symptomatic disease in 50% of these patients.[93] Most gastric ulcers are self-healing and are not responsible for major adverse gastrointestinal events. Mechanisms leading to the formation of peptic ulcer associated with NSAID therapy involve mucosal damage by means of topical injury, systemic effects from prostanoid inhibition, decreased mucosal blood flow, altered secretion of mucus and bicarbonate, and impairment of nitric oxide–mediated capillary blood flow resulting in microvascular ischemia.[99]

Studies suggest that the presence of *Helicobacter pylori* increases the risk for gastroduodenal ulcers and gastrointestinal complications in NSAID users. The combination of *H. pylori* together with the use of NSAIDs accounts for the etiology of about 90% of peptic ulcer disease.[100] An *H. pylori* infection elicits an inflammatory response leading to cytokine and neutrophil production and lymphocyte infiltration in the gastric mucosa. The combination of the *H. pylori* infection and the use of a COX-2 inhibitor, nonselective NSAID, or low-dose aspirin can also lead to increased risk of a bleeding peptic ulcer.[101] Eradication of the *H. pylori* infection is indicated in all patients with a history of ulcer, but this strategy alone is insufficient to reduce the NSAID-associated risk for ulcer and complications from the ulcer.[102]

Overall, the number of patients using NSAIDs who are at risk for gastrointestinal events is increasing. As the population ages, more patients will experience osteoarthritis, rheumatoid arthritis, chronic back pain, chronic musculoskeletal injuries, and migraine. The elderly are especially at risk for gastrointestinal events, including serious complications. Gastrointestinal problems will no doubt increase as the use of the traditional nonselective NSAIDs in the United States increases because of the concern for cardiovascular complications associated with the COX-2 inhibitors.

Balancing the risks and benefits of treatment with NSAID therapy must be an important part of the therapeutic decision-making process. The patient at risk should be identified so that concerns for gastrointestinal toxicity can be minimized (Table 3). The clinician has the responsibility to proactively manage any risk

factors if possible.[103–106] The greatest relative risk factor for gastrointestinal complications exists during the first month of therapy. Even though dyspepsia and other upper gastrointestinal symptoms are commonly associated with the use of NSAIDs, these symptoms do not appear to predict the development of a more serious gastrointestinal event.[107] A wide range of patients are also treated with both aspirin and an NSAID, increasing the risk for a gastrointestinal event. Evidence is lacking that a selective NSAID is superior to a nonselective NSAID in patients taking aspirin. A prospective, randomized, controlled trial is needed to determine if a selective NSAID plus aspirin is associated with lower rates of gastrointestinal complications.

Guidelines have been published and are helpful in guiding selection of NSAID therapy based on a patient's risk factors, as well as the use of ulcer-preventing strategies (Table 4).[108] Strategies include using a non-NSAID analgesic (acetaminophen), but this may not be feasible clinically. Other strategies include using the minimum effective dose of an NSAID for the shortest time needed. Patients identified with one or more risk factors for NSAID-induced gastrointestinal injury should be treated with preventive therapy. The use of COX-2 inhibitors may reduce the risk for gastrointestinal events; however, this benefit is negated if the patient is using aspirin, even at low doses.

Misoprostol has been shown in clinical studies to be effective in reducing the occurrence of serious upper gastrointestinal complications in patients taking continuous NSAID therapy.[109, 110] However, the drug is not well tolerated, and compliance to the drug regimen is poor due to frequent dosing. Comparative studies suggest that PPIs are more effective than misoprostol in treating an established ulcer.[111]

Sucralfate inhibits pepsin activity in gastric fluid and protects the ulcer, which in turn promotes healing. A study supports its efficacy in the treatment of NSAID-associated duodenal ulcer when the NSAID is discontinued; however, the drug is not effective in treating or preventing gastric ulcers associated with the use of NSAIDs.[112] Its use is therefore not recommended.

The histamine receptor type-2 (H_2)-antagonist famotidine is effective in preventing ulcers in patients taking NSAIDs, as demonstrated in a comparison of famotidine and placebo in patients receiving long-term NSAID therapy. However, the use of H_2-antagonists is generally not recommended for routine prophylaxis of asymptomatic patients. These agents may mask dyspepsia associated with mucosal injury. The H_2-antagonists are also less effective in healing gastroduodenal ulcers compared with a PPI, both when continuing or discontinuing the NSAID. The H_2-antagonists are also less effective in preventing recurrence of a new ulcer, as compared with a PPI.[113, 114]

Studies support the use of preventive PPI therapy along with the NSAID to reduce the frequency and severity of upper gastrointestinal symptoms.[115–118] The clinician should be aware, however, that PPI therapy protects only mucosa in the proximal gastrointestinal tract, and so injury to the bowel may still occur. If a patient develops an ulcer and requires active treatment, discontinuation of the NSAID is the best strategy. In clinical practice, this course may not be possible. Therefore, the use of a PPI is recommended over the use of an H_2-antagonist to promote the successful treatment and subsequent healing of

Table 3. Risk Factors for Gastrointestinal Events Associated with NSAID Therapy

	Risk Level for Gastrointestinal Events		
Risk Factor	Low	Moderate	High
Age (yrs)			
< 60	X		
60–64		X	
≥ 65			X
Combination therapy with NSAID			
Low-dose aspirin	X		
Anticoagulants	X		
Corticosteroids	X		
Other NSAIDs	X		
Type of NSAID			
Diclofenac	X		
Ibuprofen < 1200 mg/day	X		
Piroxicam			X
Ketoprofen			X
Ketorolac			X
Duration of NSAID therapy (mo)			
< 1			X
1–3		X	
> 3	X		
Helicobacter pylori infection	X		
Lifestyle			
Smoking and alcohol use[a]	X		
History of dyspepsia	X		

NA = not applicable.
[a]Smoking and alcohol use contribute to risk but are not considered independent risk factors.
Adapted from reference 103.

Table 4. Consensus Treatment Strategies Associated with Gastrointestinal Risk Factors and Risk Levels

Risk Level for Gastrointestinal Complications	Protective Strategy
None	Monotherapy with the least ulcerogenic agent at the lowest effective dose for the shortest duration
Low	Monotherapy with the least ulcerogenic nonselective NSAID at the lowest effective dose for the shortest duration
Moderate (advanced age or 1–2 risk factors)	Nonselective NSAID + proton pump inhibitor or misoprostol, or COX-2 inhibitor (celecoxib) for limited duration at lowest effective dose
High, or previous ulcer complications, or ≥ 2 risk factors	COX-2 inhibitor (celecoxib) at lowest effective dose, or nonselective NSAID + proton pump inhibitor, or *Helicobacter pylori* eradication
Previous lower gastrointestinal bleed[a]	COX-2 inhibitor (celecoxib) at lowest effective dose

NSAID = nonsteroidal antiinflammatory drug; COX-2 = cyclooxygenase type 2.
[a]In patients with previous NSAID-induced lower gastrointestinal bleed, more data are needed before a protective strategy can be recommended.
Adapted from reference 108.

an ulcer. After initial healing of the ulcer, continued PPI treatment is associated with lower rates of ulcer recurrence than are the H_2-antagonists.[115] In high-risk patients or those using aspirin along with an NSAID, treatment with either a PPI (lansoprazole) or misoprostol maintained an ulcer-free patient longer compared with placebo.[115]

A retrospective study was conducted to ascertain whether COX-2 inhibitors were associated with a reduced risk of gastrointestinal bleeding in a managed care population.[119] The risk of gastrointestinal bleeding was not found to be significantly different for those taking a COX-2 inhibitor compared with those taking a nonselective NSAID. Another recent retrospective study investigated the risk of adverse gastrointestinal outcomes in patients taking COX-2 inhibitors or a nonselective NSAID in a primary care population in the United Kingdom.[120] No evidence was found to support the claim of increased safety with the use of COX-2 inhibitors over nonselective agents, even among high-risk users. Questions persist regarding the feasibility of treatment with either the use of a COX-2 inhibitor plus a PPI or a COX-2 inhibitor plus a PPI plus aspirin therapy.[117] Future investigation must be completed evaluating the potential benefits of a PPI plus an NSAID compared with a COX-2 inhibitor alone with respect to the risk for bleeding throughout the gastrointestinal tract.

In choosing NSAID treatments for patients with a history of gastrointestinal disease, the clinical decision process should balance treatment benefits versus risks of the NSAID and should include a review of the relative potential for gastrointestinal complications among the available agents (Table 4). For all patients, the lowest dose of NSAID that provides benefit should be used for the shortest time needed. The PPIs are recommended as first-line therapy for prevention of gastrointestinal adverse effects in the patient assessed as having one or more risk factors. It is unknown if using a selective NSAID and a PPI for high-risk patients, especially those requiring aspirin prophylaxis, would be an effective alternative for reducing risk associated with gastrointestinal complications. A recently published study suggests that adding a PPI to celecoxib in patients with a history of NSAID-induced gastrointestinal bleeding may decrease recurrence rates compared with celecoxib alone (0% vs 8.9%, 95% CI 4.1–13.7, p=0.0004).[121]

The elderly with chronic pain deserve special mention. The American Geriatrics Society position paper for treating pain in the elderly, predating the withdrawal of rofecoxib and valdecoxib, recommended the use of COX-2 inhibitors over nonselective NSAIDS; however, with these drugs becoming increasingly less available, use of opioids for persistent pain should be considered a reasonable option.[122, 123]

Hepatotoxicity

The evidence for hepatic risk associated with NSAIDs, including the frequency of clinical adverse events and laboratory abnormalities, is limited. The risks appear to be rare. However, two NSAIDs, benoxaprofen and bromfenac, were withdrawn from the U.S. market after approval because of reports of serious hepatotoxicity. Methods that reliably predict hepatic adverse events at the premarketing stage of approval are needed. This lack of reliable screens for hepatotoxicity during the clinical trial phase

challenges clinicians to remain judicious as new agents emerge.

A recent systematic review of randomized controlled trials in patients with arthritis reported only one liver-related death among 51,942 patients taking NSAIDs.[124] The rate of hospitalization due to NSAID-induced hepatotoxicity in this review was 2.7/100,000 patients. The estimated hospitalization rate from this study was close to that of an earlier epidemiologic study suggesting a rate of hospitalization for NSAID-induced hepatotoxicity of 2.3/10,000 patient-years.[125] A significant elevation of aminotransferase levels developed in less than 0.5% of patients using ibuprofen, naproxen, meloxicam, celecoxib, and valdecoxib and did not appear to be dose related. In the first review, diclofenac and rofecoxib were associated with the highest rate of aminotransferase level elevations (3.55%, 95% CI 3.12–4.03% and 1.80%, 95% CI 1.52–2.13%, respectively).[124] Of interest, the results of the second meta-analysis suggest sulindac is the only NSAID among those analyzed with a statistically significant effect on hepatic dysfunction (odds ratio 5, 95% CI 1.3–18.5).[125] These two analyses differ in that the first defined hepatic dysfunction as liver aminotransferase levels 3 or more times the upper limit of normal compared with the latter which defined hepatic dysfunction as more than 2 times the upper limit of normal. Although inherent differences in hepatotoxic risk may exist among the various classes of NSAIDs, irrespective of COX selectivity, current data do not support routine monitoring of aminotransferase levels based solely on NSAID-associated risk.

Nephrotoxicity

The nephrotoxicity of NSAIDs is well established. Although the rate of NSAID-induced nephrotoxicity has been estimated to be low (1–5%), high utilization rates of these agents result in a large number of patients at risk.[126] Fortunately, NSAID-induced renal complications are typically reversible after discontinuation of the drug.

Renal insufficiency due to enhanced vasoconstriction is the main consequence of NSAID use. Renal dysfunction results in part from the inhibition of prostaglandins normally produced in the kidney to maintain renal blood flow. Prostaglandins have a number of important roles in renal circulation, including vasodilation, renin secretion, and sodium and water excretion. Under normal circumstances in euvolemic patients, renal prostaglandins may not be critical regulatory factors. However, in the patient with compromised renal perfusion or impaired kidney function, renal prostaglandins become more critical. If vasoconstrictive forces stimulated to maintain the filtration fraction are not balanced by prostaglandin-induced vasodilation, renal failure may occur.[127, 128] The NSAIDs may produce renal adverse effects manifested by elevations of serum creatinine concentration, sodium and water retention, interstitial nephritis, hyperkalemia, papillary necrosis, proteinuria, acute renal failure, nephrotic syndrome, acute tubular necrosis, poor perfusion with renal failure, acute glomerulitis, or vasculitis.[128–130] The population at risk for renal toxicity includes patients with chronic heart failure, cirrhosis, nephrotic syndrome, or volume depletion secondary to blood loss, diuretics, or extrarenal fluid losses. Patients with underlying renal disease and the elderly are particularly susceptible to this complication. These patients often have lower albumin levels, which result in higher free drug levels; reduced total body water, which leads to a higher concentration of the NSAID; and slowed hepatic metabolism, which can also lead to higher drug levels.[127]

The NSAIDs, including COX-2 inhibitors, must be used cautiously or not at all in patients with predisposing renal conditions. It is important to monitor blood pressure, weight, and serum creatinine and potassium concentrations when appropriate, use the lowest dose possible, and consider limiting dietary salt intake.

Central Nervous System

The central nervous system adverse effects of NSAIDs are typically overlooked when considerations are made for selecting an agent. Aseptic meningitis, psychosis, and confusion can occur rarely with NSAID use, especially when used for symptomatic treatment of systemic lupus erythematosus.[131] In addition, older individuals are at increased risk of these adverse events, especially when indomethacin or the lipophilic propionic acid derivatives are used (e.g., ibuprofen or naproxen).[132] Long-term ibuprofen administration has also displayed negative outcomes in animal models after traumatic brain injury.[133]

Recommendations and Conclusion

Chronic nonmalignant pain is a major burden on the health care system, and NSAIDs frequently

Table 5. Specific Practice-Related Questions and Consensus Recommendations

Practice-Related Question	Recommendation
What role do NSAIDs have in the long-term treatment of osteoarthritis or rheumatoid arthritis?	Acetaminophen should be considered first-line therapy for symptomatic treatment of osteoarthritis. A low-dose NSAID may be considered for symptomatic treatment unresponsive to acetaminophen. The nonselective NSAID, naproxen, with a disease-modifying antirheumatic drug should be considered first-line therapy for symptomatic treatment of rheumatoid arthritis. Celecoxib, preferably at the lowest effective dose, may be considered in patients unable to tolerate naproxen. Note that NSAIDs have not been shown to slow or halt the progression of rheumatoid arthritis.
What is the role of NSAIDs for symptomatic treatment of chronic low back pain?	Due to limited availability of RCT data to support efficacy of NSAIDs for treatment of chronic low back pain and the potential for adverse drug events with prolonged exposure, NSAIDs should not be used to treat chronic low back pain.
What is the role of NSAIDs for symptomatic treatment of fibromyalgia syndrome?	Due to the lack of RCT data to support efficacy of NSAIDs for treatment of fibromyalgia syndrome, these agents should not be used as primary therapy for this condition.
What is the role of NSAIDs in the treatment of painful peripheral neuropathies?	Due to the lack of RCT data to support efficacy of NSAIDs for treatment of painful peripheral neuropathies, these agents should not be used as primary therapy for these conditions.
What are the gastrointestinal risks associated with NSAIDs when used for prolonged periods to treat chronic pain syndromes, and how should these risks be addressed?	Data from RCTs suggest that even selective NSAIDs when used for extended durations or given concurrently with aspirin for cardioprotection may lose the benefit of reduced risk of gastrointestinal toxicity. Naproxen, with a PPI, should be used to treat chronic pain syndromes in which NSAID therapy is indicated and at least one risk factor for gastrointestinal complications is present. In addition, patients receiving cardioprotective doses of aspirin should receive an NSAID + PPI, should NSAID therapy be warranted. Celecoxib, at the lowest effective dose, may be considered a second-line alternative to minimize gastrointestinal toxicity.
What are the cardiovascular risks of NSAIDs in chronic pain syndromes?	A dearth of information precludes solid recommendations. Patients with rheumatoid arthritis may be at an increased risk for cardiovascular events. Ibuprofen or naproxen, given with a PPI, appears to convey the safest alternative when NSAIDs are indicated. Celecoxib, at the lowest effective dose, may be a safe alternative when considering a selective NSAID, based on preliminary data. Note that ibuprofen should be administered more than 4 hours before or more than 2 hours after cardiovascular protective dosing of aspirin.
Are NSAIDs associated with hepatic toxicity, and should liver function tests be monitored regularly when using NSAIDs to treat chronic pain syndromes for prolonged periods?	Baseline and periodic monitoring of liver function tests should be performed during prolonged NSAID therapy. No data from RCTs suggest that NSAIDs, other than sulindac or diclofenac, are hepatotoxic.
What, if any, renal toxicities are associated with NSAIDs?	Data from RCTs suggest both nonselective and selective NSAIDs adversely affect fluid-dependent renal hemodynamics. NSAIDs should be avoided in clinical scenarios in which renal perfusion may be compromised.
Should concern of central nervous system toxicity preclude the use of NSAIDs for prolonged periods in persons with chronic pain syndromes?	Central nervous system toxicities associated with NSAID use are rare. Consider celecoxib at the lowest effective dose for geriatric patients who are unable to tolerate ibuprofen or naproxen, with PPIs.

NSAID = nonsteroidal antiinflammatory drug; RCT = randomized controlled trial; PPI = proton pump inhibitor.

are used to treat the many chronic pain syndromes. The effectiveness and safety profiles of NSAIDs for these indications vary. Consensus recommendations on the use of these agents are provided in Table 5.

Data continue to come forth regarding the safety risks of the newer COX-selective and traditional NSAIDs. Although the gastrointestinal adverse effects of NSAIDs have been well described, the potential cardiovascular risks continue to evolve. The cardiovascular risks first appeared to be a class effect of the COX-2 inhibitors. Additional studies have further implicated several nonselective agents, although the underlying etiology of this remains unclear. At this point, definitive recommendations regarding which agents are safe for long-term use are premature.

The American Heart Association recently

published a statement regarding the use of NSAIDs and the associated risks in those with known cardiovascular disease or risk factors for ischemic heart disease. This group recommends acetaminophen, aspirin, tramadol, short-term opioid analgesics, or nonacetylated salicylates as first-line therapy for those with known cardiovascular risk factors. Further options, should these fail or be contraindicated, include nonselective NSAIDs, NSAIDs with some COX selectivity, and finally selective NSAIDs. Unfortunately, classification of these agents into these groups based solely on COX-2:COX-1 selectivity ratios may prove difficult at best. In addition, pharmacodynamic effects of these agents may change with respect to prostaglandin E_2 inhibition, prostacylcin (prostaglandin I_2) inhibition, and prevention of remodeling or collateralization based on dose achieved.

Gastrointestinal toxicity with prolonged NSAID use is difficult to address as major events typically occur within the early months of treatment. In addition, dyspepsia correlates poorly with pathologic tissue damage, ulceration, and gastrointestinal bleeding. This makes screening and monitoring for this adverse effect tenuous at best. The consensus recommendations outlined in Table 4 provided in this article should be followed, with the propensity to err on the side of conservatism when considering preventive PPI concurrent therapy. Regardless, positive efficacy data from randomized controlled trials must be present before selecting any analgesic. The cadre of risks associated with prolonged NSAID use must be addressed, as well as the benefits, on a patient-by-patient basis.

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