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NSAIDs for Musculoskeletal Pain Management: Current Perspectives and Novel Strategies to Improve Safety

James W. Atchison, DO; Christopher M. Herndon, PharmD, BCPS, CPE, FASHP; and Erica Rusie, PharmD

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Target Audiences

This CME/CE activity is designed to meet the educational needs of pharmacists, physicians, nurse practitioners, and nurses.

Learning Objectives

- Assess patient-specific risk factors in selecting NSAIDs for mild-to-moderate musculoskeletal pain
- Incorporate risk/benefit analysis in decision making about NSAID use
- Use evidence-based guidelines for selecting NSAID therapy and applying strategies to prevent complications
- Evaluate the efficacy, safety, and pharmacological profile of new and emerging NSAID formulations

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James W. Atchison coauthored this supplement under contract with PRIME and reported a consulting relationship with Mallinckrodt Pharmaceuticals. Christopher M. Herndon serves on the advisory boards of Novartis Pharmaceuticals, Mallinckrodt Pharmaceuticals, and Incline Therapeutics and supports promotional education with Millennium Pharmaceuticals. Erica Rusie is an employee of PRIME, a medical education company that receives grants and funding for educational programs from government agencies and various pharmaceutical manufacturers. Steven Stanos is a consultant for myMatrixx and serves on advisory boards for Mallinckrodt Pharmaceuticals and Pfizer. Donna Chiefari and Kathleen Jarvis report no financial interests or other relationships with companies with commercial interests in pain medications or other potential conflicts of interest related to the subjects in this supplement.

NSAIDs for Musculoskeletal Pain Management: Current Perspectives and Novel Strategies to Improve Safety

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ABSTRACT

BACKGROUND: Musculoskeletal disorders are a growing burden on the health care system in the United States. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to assist in the management of mild-to-moderate musculoskeletal pain. After the withdrawal of rofecoxib because of cardiovascular toxicity, the safety of these agents became a topic of controversy and confusion. Recent evidence is facilitating a better understanding of the risks and mechanisms by which NSAIDs cause injury. In an effort to raise awareness, this review addresses the current challenges, recent progress, and novel strategies for improving tolerability. With new data to help guide decision making and the anticipated increase in pharmacological options for managing musculoskeletal pain, the role of the managed care professional is particularly important in this evolving field.

OBJECTIVES: To review recommendations for the appropriate use of NSAIDs, incorporate risk/benefit analysis into decision making, and evaluate the efficacy and safety of recently approved and emerging NSAID formulations.

SUMMARY: Musculoskeletal-related conditions are a major public health burden. NSAIDs are among the most commonly used medications for musculoskeletal conditions. Since the introduction of selective cyclooxygenease-2 (COX-2) inhibitors (or coxibs), there has been ongoing discussion and debate about the safety of all NSAIDs. Current available evidence suggests both traditional NSAIDs and coxibs increase the risk of gastrointestinal and cardiovascular toxicity; however, with proper risk assessment, these dangers can be limited. Moreover, new and emerging NSAID formulations and delivery systems aim to enhance the effectiveness and reduce the toxicity associated with these anti-inflammatory agents.

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Musculoskeletal disorders affect millions of people of all ages around the world.[1] This nonspecific term can pertain to all conditions that may cause pain in the musculoskeletal system, which includes muscles, nerves, tendons, joints, and cartilage.[2] Musculoskeletal disorders can be broadly categorized as diseases of the joints, bone, cartilage, spine, or back.[3] They include joint diseases such as osteoarthritis and rheumatoid arthritis; back and neck pain; osteoporosis and related fractures; soft tissue rheumatism (e.g., tendinitis, bursitis, and myofascial pain); injuries from sports or in the workplace; and trauma related to motor vehicle accidents.

The pain brought on by musculoskeletal conditions can significantly impact quality of life (e.g., ability to work, sleep, and perform physical and social activities).[1] Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed for musculoskeletal pain, but following the withdrawal of rofecoxib because of cardiovascular toxicity, their safety has been in question.[4-6] Progress has been made over the past decade to answer unresolved questions regarding their safety, efficacy, and mechanisms underlying their risks.[7] New therapeutic options formulated with submicron drug particles and hybrid molecules have resulted in a renewed interest in this commonly used but potentially dangerous class of drugs.

Epidemiology and Impact

Musculoskeletal disorders are recognized by the World Health Organization (WHO), the United Nations, and the Centers for Disease Control and Prevention (CDC) as a problem of global proportions.[1] In a 2012 issue of *The Lancet*, the Global Burden of Disease Study of 2010 revealed that musculoskeletal diseases are the second greatest cause of disability in the world.[1,8] An estimated 1.7 billion people worldwide are affected by a musculoskeletal condition. One in two adults reported suffering from chronic or recurring musculoskeletal pain.[8]

In the United States, musculoskeletal-related conditions affect more than 30% of adults.[8] They are associated with the largest number of years lived with disability.[8,9] According to *The Burden of Musculoskeletal Diseases in the United States*, low back pain is the most common reported musculoskeletal condition; however, chronic joint pain (joint pain for 3 months or more) is approaching a similar level of prevalence.[8] In 2011, 61.6 million Americans reported to have chronic joint pain; 62 million reported low back pain; and 31.4 million reported neck pain.[8] The prevalence and consequences of pain differ between men and women. Comparisons are difficult due to a wide range of influencing factors such as pain threshold and multiple comorbidities.[10] In older adults, women are more likely than men to develop musculoskeletal pain and less likely to have the pain resolved.[10] Despite the high prevalence of musculoskeletal conditions, research funding is low, likely due to relatively low mortality rates.[8]

Musculoskeletal conditions are very common and impact both the individual and society. Considering death and disability, musculoskeletal conditions have the fourth greatest impact on the health of the world population, closely following cardiovascular and circulatory diseases, tumors, and mental disorders.[1,8] Those musculoskeletal conditions with the greatest impact on society include low back and neck pain, arthritis and joint pain, osteoporosis, and musculoskeletal injuries. In the United States, annual direct and indirect costs are an estimated $950 billion. The burden has increased by 45% over the past 2 decades, a trend that is forecasted to continue.

Assessment and Management of Mild-to-Moderate Musculoskeletal Pain

This section provides a general overview of approaches to assessing and treating pain associated with musculoskeletal disorders. A brief review of established guidelines for managing mild-to-moderate pain is included.

TABLE 1 Pain Assessment Tools

Unidimensional Pain Assessment Tools
• Visual Analog Scale
• Verbal Rating Scale
• Faces Pain Rating Scale
• Numeric Rating Scale
Multidimensional Pain Assessment Tools
• McGill Pain Questionnaire (long and short)
• Brief Pain Inventory (long and short)
• Pain Disability Index
• Chronic Pain Grade Scale
• Short Form-36 Bodily Pain Scale
• Measure of Intermittent and Constant Osteoarthritis Pain
• Roland Morris Disability Questionnaire
• Hospital Anxiety and Depression Questionnaire

Clinical Assessment of Pain Associated with Musculoskeletal Disorders

Clinical features vary depending on the type of musculoskeletal disorder. Generally, the symptoms are pain, tenderness, weakness, stiffness, limited range of motion, and peripheral nerve irritation.[11] Pain may be localized, regional, or widespread. Musculoskeletal pain is typically classified as acute or chronic. Acute musculoskeletal pain is short in duration, typically less than 1 month. Chronic pain persists for longer periods and is often more challenging to treat. Unique clinical features can help distinguish the various types of musculoskeletal conditions. For example, osteoarthritis typically involves larger joints in a nonsymmetrical nature, whereas rheumatoid arthritis is usually more symmetrical.[12]

A complete history and physical examination remain the most crucial tools for diagnosing musculoskeletal pain.[11] Obtaining a comprehensive medical history of the patient is the first step and should include assessing the pain intensity and characteristics. Questions to determine the onset, location, duration, intensity, aggravating and relieving factors, previous treatment, and a general description are important in this component of the diagnosis. "Red flags," including trauma, unexplained weight loss, unexplained fever, immunosuppression, history of cancer, intravenous drug use, prolonged use of corticosteroids, osteoporosis, age greater than 70 years, and duration of pain for more than 3 months, indicate the possible presence of a more serious underlying condition. Having the patient complete a pain diagram, marking the symptomatic region, is also recommended at the initial assessment.[13] Information from the medical history regarding the particular area of pain can be helpful in focusing the physical examination.[11] During the exam, the clinician appraises the patient's physical condition, evaluating physical factors (e.g., different positions) and function (e.g., range of motion).

The patient's perceived level of pain can be determined using a pain assessment tool. These tools may be unidimensional (assessing a single dimension of pain) or multidimensional (assessing multiple aspects of pain; Table 1). Experts recommend multidimensional tools for patients with chronic and complex conditions because they can provide information about the characteristics of pain and the effects on daily life. The use of 1 standardized tool promotes consistency of care and communication among providers.

Blood tests are generally not required in patients presenting with mild-to-moderate musculoskeletal pain.[14] However, they may be ordered in patients with signs or symptoms of a more serious underlying condition. Elevated acute phase inflammatory markers—C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and antinuclear antibodies—can help rule out autoimmune-associated rheumatologic conditions. Magnetic resonance imaging (MRI), X-rays, computed tomography (CT) scan, and joint fluid testing can also be utilized in order to confirm or gather more information.[14]

Management of Mild-to-Moderate Pain

A wide variety of treatment options are available to manage musculoskeletal pain. Evidence-based approaches include nonpharmacological and pharmacological interventions. Generally, treatment is tailored to fit the needs and risk factors of the individual.[15] Care for patients with chronic pain can involve a multidisciplinary team that includes primary care physicians, medical specialists, psychiatrists, psychologists, physical therapists, occupational therapists, social workers, pharmacists, relaxation therapists, vocational counselors, and nurses.

Nonpharmacological Treatment. Multiple nonpharmacological therapies are available for the management of musculoskeletal pain disorders.[16] These measures can be divided into physical and psychosocial modalities. Physical measures include bed rest; exercise; local heat or cold therapy; manual therapies (spinal manipulation, massage, and mobilization techniques); and stimulation techniques (acupuncture, transcutaneous electrical nerve stimulation [TENS], and percutaneous electrical nerve stimulation). Psychosocial interventions include patient education, relaxation techniques, biofeedback, guided imagery, support groups, family counseling, and psychotherapy. Practices such as tai chi—which includes specialized movements and breathing techniques, combining both physical and psychosocial measures—have been shown to improve functional ability, reduce pain, and improve psychosocial health in patients with musculoskeletal conditions.[17]

Dietary supplements may be an alternative treatment for patients wary of prescription medications. Glucosamine and chondroitin, methylsulfonylmethane (MSM), and omega-3 fatty acids have been shown to reduce pain and improve physical function in patients with musculoskeletal-related conditions such as osteoarthritis and low back pain.[18-21] Because dietary supplements are not regulated by the U.S. Food and

Drug Administration (FDA), caution is warranted when using or recommending these products. Additionally, while well-controlled prospective studies exist to support many of these therapies, the data are largely equivocal, precluding strong recommendations from either respective guideline panels or these authors.

Pharmacological Treatment. A variety of oral and topical analgesic medications are available for the treatment of musculoskeletal disorders and injuries.[22,23] Analgesics include opioids, nonopioids, and adjuvant analgesics. They are available in many forms, both over-the-counter (OTC) or by prescription. Nonopioid analgesics include acetaminophen, salicylates, and NSAIDs. Adjuvant analgesics (or coanalgesics) are drugs with primary indications other than pain but have secondary effects of analgesia.[24] They include muscle relaxants, anticonvulsants, antidepressants, corticosteroids, and alpha-2 adrenergic agonists.[25-27] Duloxetine, a serotonin-norepinephrine reuptake inhibitor, recently received FDA approval for chronic musculoskeletal pain, based on studies in knee osteoarthritis and low back pain.

Guidelines and Recommendations for the Management of Mild-to-Moderate Pain. Several international health organizations including the WHO and the International Association for the Study of Pain (IASP) promote the concept of pain management as a human right.[28,29] The WHO offers a stepwise approach in the management of pain disorders with pharmacological treatment.[29] In summary, step 1 begins with the use of a nonopioid analgesic (e.g., acetaminophen or an NSAID) at the lowest effective dose for reducing pain and inflammation. The dose may then be titrated or gradually increased based on the patient's response and tolerance. If adequate pain relief is not achieved with the maximum dose of the nonopioid analgesic, a weak opioid (e.g., tramadol or codeine) may be substituted or added. A strong opioid (e.g., morphine or oxycodone) can replace the weak opioid when pain persists.[29]

Evidence-Based Treatment Practices Involving NSAIDs: Informed Decision Making

NSAIDs are among the most commonly used medications for musculoskeletal conditions because of their known effectiveness as anti-inflammatory and analgesic agents. A recent study in *The Journal of Pain* found that NSAIDs were the most preferred and prescribed drugs for chronic pain.[5] In 2012, 98 million prescriptions were filled for NSAIDs, and approximately 23 million people in the United States used OTC NSAIDs regularly.[30,31] Ibuprofen is the most commonly used NSAID in the United States, while diclofenac is the most popular throughout the world.[4,6,30]

NSAIDs have anti-inflammatory, analgesic, and antipyretic properties.[32] They are indicated for the treatment of mild-to-moderate pain in various acute and chronic inflammatory conditions. Their efficacy has been established in numerous acute and chronic pain conditions including osteoarthritis, rheumatoid arthritis, low back pain, neck pain, headache, dysmenorrhea, and gout. NSAIDs are generally preferred over opioids because of their established effectiveness and limited potential for abuse.

NSAIDs comprise traditional NSAIDs and cyclooxygenase-2 (COX-2) inhibitors (or coxibs). All NSAIDs inhibit the production of prostaglandins by inhibiting the activity of PGG/H synthase, also known as cyclooxygenase (COX).[33] COX exists in 2 isoforms (COX-1 and COX-2), which differ in tissue expression and regulation.[33] The therapeutic effects of NSAIDs are attributed to inhibition of COX-2 in inflammatory sites. Specificity to the COX isoform is a key factor that influences both efficacy and safety.

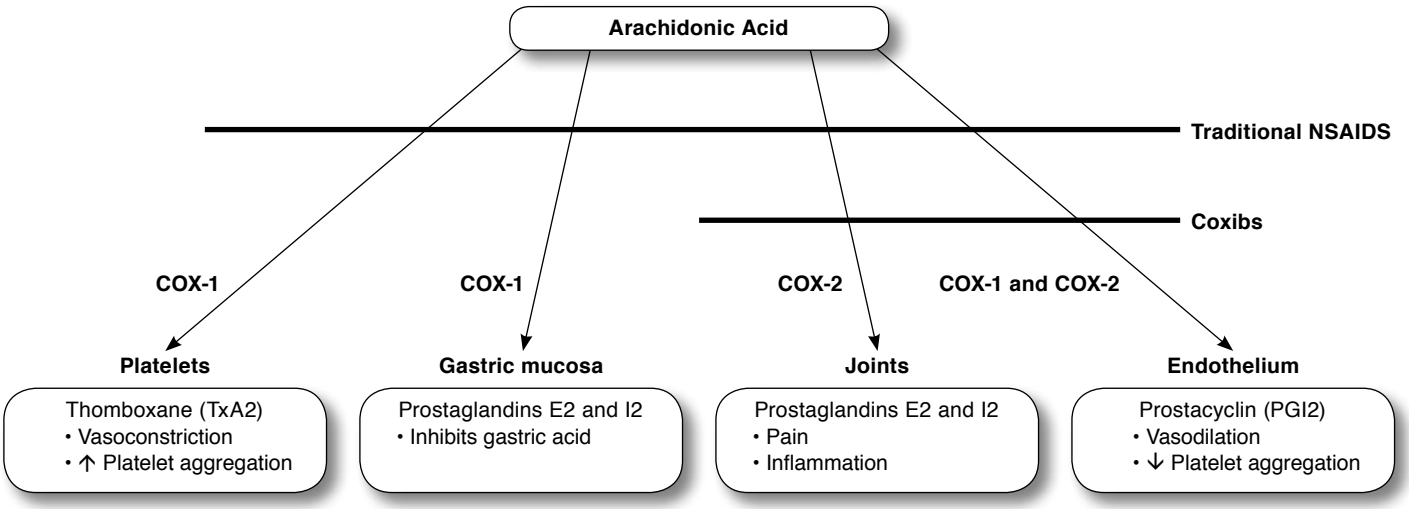
NSAIDs are available both OTC and by prescription and in oral and topical formulations. Nonprescription aspirin, ibuprofen, and naproxen are sold at low doses and can be found in combination products used for pain and fever or cough and cold. Many oral formulations are available as generic drugs. In 2007, a topical diclofenac patch was approved for the treatment of pain. Diclofenac is the first and only NSAID approved for topical use.[34] Currently, 3 topical formulations, all salts of diclofenac, are commercially available in the United States for use in pain: 1.3% diclofenac epolamine transdermal patch, 1% diclofenac sodium gel, and diclofenac sodium 1.5% topical solution.[35-37] The transdermal patch is approved for acute musculoskeletal injury (minor sprains, strains, and contusions), and the solution and gel are approved for the treatment of osteoarthritis pain.[35-37]

Topical NSAIDs were developed as an alternative to oral NSAIDs and may be beneficial for localized pain.[38] A meta-analysis evaluating 34 studies from 7,688 adults with chronic musculoskeletal pain found that topical NSAIDs provided adequate pain relief, equivalent to oral NSAIDs for hand and knee osteoarthritis.[39] Currently, there is a lack of sufficient evidence comparing oral and topical NSAIDs for other chronic pain conditions. Systemic absorption is lower with topical agents; thus, they are associated with fewer adverse events. The incidence of local adverse events, however, is increased with topical NSAIDs. In the past 5 years, various updated guidelines have included recommendations for the use of topical NSAIDs, particularly in patients considered at gastrointestinal or cardiovascular high risk.[23,40,41]

Mechanism of Action

Felix Hoffman, a German chemist, is credited with being the first to synthesize aspirin from salicylic acid, a constituent of the willow bark tree.[42] This development in 1897 led to widespread use; however, the mechanism of action was unclear until 1971 when pharmacologist John Vane determined that aspirin blocks the action of COX.[43] This discovery ignited

FIGURE 1 NSAIDs: Mechanism of Action



NSAIDs inhibit the production of prostaglandins (PG) by inhibiting the activity of COX from arachidonic acid. COX occurs in 2 isoforms (COX-1, COX-2). COX-1, the constitutive isoform, is present in many tissues and is associated with the production of prostanoids for "housekeeping" functions. COX-2 is considered the inducible isoform, undetectable in most tissues. This isoform is expressed at sites of inflammation and is associated with the production of pro-inflammatory prostanoids. The products of arachidonic acid metabolism are thromboxane A2, PGE2, and PGI2. Thromboxane A2 is the main prostanoid produced by platelets, and PGI2 is synthesized by vascular endothelium. Thromboxane A2 acts as a vasoconstrictor and promoter of platelet aggregation, whereas PGI2 is a vasodilator that inhibits platelet aggregation. Inhibition of COX-1 or COX-2 tips the PGI2-thromboxane A2 balance. In the gastrointestinal system, COX-1 provides cytoprotective PGE2 and PGI2. Suppression of these prostaglandins results in increased gastric acid and pepsin production and decreased gastric mucus secretion. COX-2 is responsible for increased prostaglandin production in inflamed joints. Traditional NSAIDs and coxibs both inhibit COX-2 and, thus, achieve similar anti-inflammatory activity.[43,48]

COX = cyclooxygenase; coxibs = cyclooxygenease-2 (COX-2) inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs.

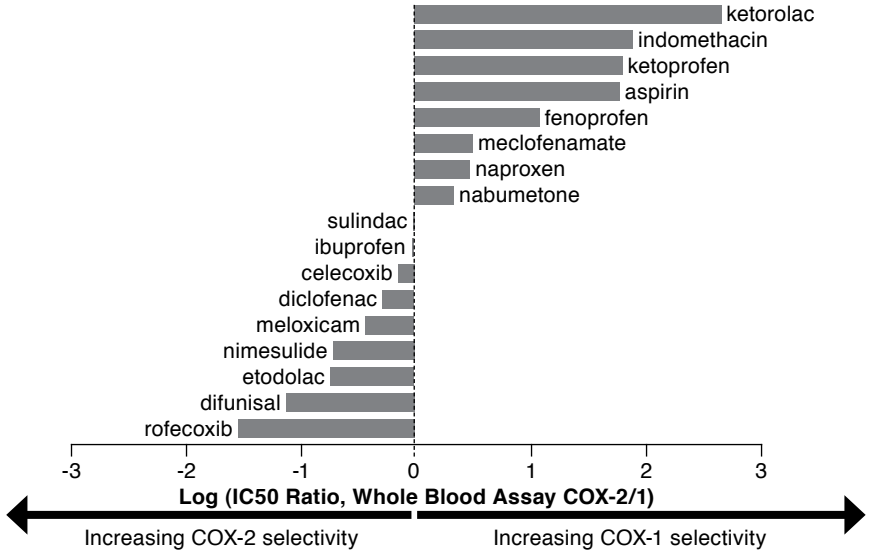
research into a better understanding of this mechanism and the development of similarly acting drugs.

In addition to COX-1 and COX-2, an isoform called COX-3, derived from COX-1, is expressed in the cerebral cortex and heart.[44] COX-1 is found in almost all tissues under basal conditions and is responsible for the production of prostaglandins involved in gastric mucosal integrity.[43,45] COX-1 is referred to as a "constitutive," whereas COX-2 is considered to be "inducible," expressed during various conditions such as inflammation.[46] Unlike COX-1, COX-2 expression is usually minimal and undetectable in most tissues; however, when activated, COX-2 regulates prostaglandin production that mediates inflammation, pain, and fever.

NSAIDs produce analgesic and anti-inflammatory effects via central and peripheral actions.[45] Their primary mode of action involves the inhibition of the COX enzyme.[43,47] NSAIDs inhibit the synthesis of prostaglandins by preventing the substrate arachidonic acid from binding to the COX enzyme active site. Suppression of PGG/H synthase thus prevents the formation of PGE2, PGI2 (prostacyclin), and thromboxanes.[47,48] Most traditional NSAIDs inhibit both COX isoforms but vary on degree of selectivity. Only COX-1 is expressed in platelets; thus, a COX-2 selective agent is one that lacks inhibitory effects on platelet function (Figure 1).[46]

NSAIDs have similar chemical structures, although there are key differences in pharmacokinetic properties, analgesic efficacy, and COX selectivity.[32,49] Most NSAIDs are well absorbed from the gastrointestinal tract following oral ingestion. They are highly bound to plasma proteins and thus have a small volume of distribution. NSAIDs are metabolized in the liver and excreted in the urine as metabolites. Plasma half-lives vary considerably, ranging from 15 minutes to more than 70 hours. The analgesic efficacy of NSAIDs also varies considerably. Ketorolac and diclofenac have demonstrated comparable analgesic efficacy to that of low-dose opioids, effectively treating postsurgical pain and acute musculoskeletal pain. According to a comparative effectiveness review published by the Agency for Healthcare Research and Quality (AHRQ) Effective Healthcare Program, at therapeutically equivalent doses, the clinical efficacy of the NSAIDs is similar.[32] No differences were found in efficacy for the treatment of osteoarthritis pain between a traditional NSAID and another traditional NSAID or between a traditional NSAID and a coxib.

FIGURE 2 NSAIDs: COX-2 Versus COX-1 Selectivity



Selectivities of NSAIDs and coxibs as inhibitors of COX-1 and COX-2 are displayed as the ratio of IC50 concentrations. Inhibitor curves were developed using IC50 values in whole blood assay.[176] The IC50 ratios are expressed logarithmically so that the "0 line" represents unity (i.e., compounds that are equiselective for COX-1 and COX-2). Compounds appearing to the right of the line are more COX-1 selective; those to the left of the line are more COX-2 selective.

COX = cyclooxygenase; coxibs = cyclooxygenase-2 (COX-2) inhibitors; IC50 = 50% inhibitory concentration; NSAIDs = nonsteroidal anti-inflammatory drugs.

Both traditional NSAIDs and coxibs inhibit COX but vary in affinity to the different isoforms.[50,51] The selectivity of a particular drug is dependent on its concentration. The degree of selectivity is expressed as a ratio of the 50% inhibitory concentration (IC50) value of COX-2 to the IC50 value of COX-1 in whole blood (Figure 2). Certain traditional NSAIDs such as meloxicam, nimesulide, and etodolac are slightly selective for COX-2.[52] Ibuprofen and naproxen are generally nonselective. Other agents such as ketoprofen, flurbiprofen, and aspirin have higher selectivity for inhibiting COX-1. Based on in vitro studies measuring COX-2 inhibition, there is considerable overlap between certain coxibs (e.g., celecoxib) and certain traditional NSAIDs (e.g., diclofenac, meloxicam).

Safety Concerns

The coxibs were the successors to NSAIDs, originally intended to provide pain relief and reduce inflammation without causing gastrointestinal side effects.[53] Early results from 2 large clinical trials, the Celecoxib Long-term Arthritis Safety Study (CLASS) and Vioxx Gastrointestinal Outcomes Research (VIGOR), showed that the coxibs celecoxib and rofecoxib were effective as anti-inflammatory agents and were shown to have a significantly lower risk of serious gastrointestinal complications relative to traditional NSAIDs.[54,55] Although the coxibs were found to be effective and have higher gastrointestinal tolerability, post hoc analysis of clinical trial data revealed alarming cardiovascular safety concerns. The VIGOR study revealed a 5-fold increase in cardiovascular events with rofecoxib compared with naproxen.[54] In late September 2004, the 3-year Adenomatous Polyp Prevention of Vioxx (APPROVe) trial, evaluating the efficacy of rofecoxib 25 milligrams (mg) in preventing recurrence of colorectal polyps in patients with a history of colorectal adenomas, was halted 2 months early because of data indicating an increased risk of serious cardiovascular events, including heart attacks and strokes.[56] These findings prompted the manufacturers of rofecoxib to voluntarily withdraw the drug from the U.S. market.[57]

Safety was increasingly a focus of concern, particularly for celecoxib. Results from the CLASS trial did not show the same risk with celecoxib.[55] However, interim results from the Adenoma Prevention with Celecoxib (APC) trial in 2004 suggested an increased cardiovascular risk compared with placebo and led to the decision to stop the trial.[58] Similar analysis was applied to another trial, Prevention of Colorectal Sporadic Adenomatous Polyps (PreSAP), but the risk was not found to be statistically significant.[59] Investigators advised that the findings from the APC and PreSAP trials be read with caution, as neither trial was designed or powered to evaluate cardiovascular risk.[60] Later that year, the Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT), comparing naproxen, celecoxib, and

placebo, showed an increased cardiovascular and cerebrovascular risk with naproxen but not with celecoxib.[61]

Questions began to arise regarding the cardiovascular risks associated with all coxibs, and emerging drugs were affected by the controversial data.[62,63] On April 7, 2005, the FDA announced its request to the manufacturers of valdecoxib to withdraw the drug from the market after determining that "the overall risk versus benefit profile for the drug is unfavorable."[64] In addition, the agency requested manufacturers of all other NSAIDs (prescription oral, topical, and OTC) to revise their labels to include the "black box" warning about the potential cardiovascular and gastrointestinal risks. After the withdrawal of rofecoxib and valdecoxib, celecoxib remained on the market in the United States, and research surrounding the safety of NSAIDs continued.[65,66] Many experts were not convinced that the cardiovascular effects of rofecoxib represented a class effect.[54,67] In addition, the debate continued regarding the association between COX-1 and COX-2 selectivity and risks, as well as factors that modulate drug response.[68-70]

Nine years after the withdrawal of rofecoxib, research is providing clarity.[7,32] In 2011, the comparative effectiveness review published by AHRQ noted that the cardiovascular safety of traditional NSAIDs (with the exception of naproxen and low-dose ibuprofen) was similar to that of coxibs. Recently, results from a large meta-analysis supported this conclusion. In the May 2013 issue of *The Lancet*, the international consortium known as the Coxib and traditional NSAID Trialists (CNT) Collaboration released their findings from a meta-analysis of 639 clinical trials that included more than 350,000 NSAID users.[7] The investigators assessed cardiovascular and gastrointestinal risks of certain NSAID regimens among various types of patients, particularly those considered to be high risk for vascular disease. Naproxen appears to offer the most favorable cardiovascular safety profile, moderately superior to that of other traditional NSAIDs and coxibs.[7,32] Researchers of the CNT Collaboration explained that once baseline characteristics and risks are obtained, these adverse events can be predicted.[7] They urged clinicians to broaden their view on NSAIDs and include all potential concerns and benefits in their decision making.

Gastrointestinal Adverse Events. Long-term use of NSAIDs is the second most common cause of peptic ulcers and can lead to further complications including bleeding, perforation, and obstruction.[53,71] Damage can occur to the upper gastrointestinal tract, small intestine, and large intestine.[53,72] The damaging effects of NSAIDs on the gastrointestinal tract have been well documented and characterized. Results from the comparative effectiveness review by AHRQ suggested no difference between traditional NSAIDs and coxibs at commonly used dosages.[32] In the CNT Collaboration study, both traditional NSAIDs and coxibs were associated with an increased risk of upper gastrointestinal complications compared with placebo (rate ratio [RR] of 1.81, 95% confidence interval [CI] = 1.17-2.81, $P = 0.007$ for coxibs; RR 1.89, 95% CI = 1.16-3.09, $P < 0.011$ for diclofenac; RR 3.97, 95% CI = 2.22-7.10, $P < 0.001$ for ibuprofen; and RR 4.22, 95% CI = 2.71-6.56, $P < 0.001$ for naproxen); 2% of the complications were recorded as fatal.[7] Further, comparable analyses revealed that each coxib is associated with similar ulcer risks ($P > 0.1$).

NSAIDs with the greatest COX-1 selectivity and those at high doses are typically associated with the greatest gastrointestinal toxicity.[32] Gastric mucosal damage occurs primarily through inhibition of mucosal prostaglandin synthesis and, to a much lesser extent, direct (or topical) irritation of the gastric epithelium.[73] Inhibition of COX-1 is known to cause gastrointestinal injury. Although traditional NSAIDs inhibit both COX-1 and COX-2 isoforms, COX-1 is predominantly expressed in the gastrointestinal tract. This isoenzyme regulates the production of prostaglandins that protect the gastric mucosa by maintaining blood flow and stimulating mucus and bicarbonate secretion. Damage to the protective barrier and reduced mucus and bicarbonate production make the gastric epithelial cells more susceptible to the erosive effects of pepsin and hydrochloric acid. While gastrointestinal toxicity may occur with any NSAID at any location, the predominant concern associated with these drugs is gastrointestinal bleeding. Upper gastrointestinal bleeds (UGIB) due to NSAIDs appear to be more prevalent than lower (duodenal) gastrointestinal bleeds. Differences in likely etiologies and effectiveness of prevention strategies point to UGIB being more strongly associated with prostaglandin inhibition, while duodenal bleeds appear to be correlated with direct acid exposure.

Cardiovascular Adverse Events. After the development of coxibs, subsequent evidence showed an increased risk of vascular events with these drugs.[7,32,58-61] Further studies comparing coxibs versus traditional NSAIDs suggested that traditional NSAIDs may also be associated with a vascular hazard.[32,61] Most recently, the large meta-analysis conducted by the CNT Collaboration focused on quantifying and characterizing cardiovascular risks of NSAID regimens, particularly in patients at increased risk of vascular disease.[7] According to this study, all NSAIDs were found to increase the risk of cardiovascular events (with the exception of naproxen). The results revealed that the use of a coxib or diclofenac was associated with 3 additional vascular events per 1,000 patient-years. Major vascular events (nonfatal myocardial infarction [MI], nonfatal stroke, or vascular death) were increased by approximately one third with coxibs and diclofenac compared with placebo (RR 1.37, 95% CI = 1.14-1.66, $P < 0.001$ for coxibs and RR 1.41, 95% CI = 1.12-1.78, $P < 0.004$ for diclofenac). The risk of major coronary events (nonfatal MI or coronary death) was increased with the aforementioned drugs as well as ibuprofen (RR 1.76, 95% CI = 1.31-2.37, $P < 0.001$ for coxibs; RR 1.70, 95% CI = 1.19-2.41, $P < 0.003$ for diclofenac; and RR 2.22, 95% CI = 1.10-4.48,

TABLE 2 *Cardiovascular and Gastrointestinal Risks Associated with the Use of Traditional NSAIDs and Coxibs*

Drug	Rate Ratio of Major Vascular Events	Rate Ratio of Major Coronary Events	Rate Ratio of Hospitalization Due to Heart Failure	Rate Ratio of Upper Gastrointestinal Bleed
Diclofenac	1.41 (95% CI = 1.12-1.78; $P < 0.004$)	1.70 (95% CI = 1.19-2.41; $P = 0.003$)	1.85 (95% CI = 1.17-2.94; $P < 0.009$)	1.89 (95% CI = 1.16-3.09; $P = 0.0106$)
Ibuprofen	1.44 (95% CI = 0.89-2.33; $P = 0.14$)	2.22 (95% CI = 1.10-4.48; $P = 0.025$)	2.49 (95% CI = 1.19-5.20; $P < 0.016$)	3.97 (95% CI = 2.22-7.10; $P < 0.001$)
Naproxen	0.93 (95% CI = 0.69-1.27; $P = 0.66$)	0.84 (95% CI = 0.52-1.35; $P = 0.48$)	1.87 (95% CI = 1.10-3.16; $P < 0.02$)	4.22 (95% CI = 2.71-6.56; $P < 0.001$)
Coxib	1.37 (95% CI = 1.14-1.66; $P < 0.001$)	1.76 (95% CI = 1.31-2.37; $P < 0.001$)	2.28 (95% CI = 1.62-3.20; $P < 0.001$)	1.81 (95% CI = 1.17-2.81; $P = 0.007$)

Source: Coxib and traditional NSAID Trialists' (CNT) Collaboration, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials.[7]

CI = confidence interval; coxib = cyclooxygenease-2 (COX-2) inhibitor; NSAIDs = nonsteroidal anti-inflammatory drugs.

$P = 0.025$ for ibuprofen). Naproxen was not associated with a high risk of major vascular events (RR 0.93, 95% CI = 0.69-1.27, $P = 0.66$) or an increase in coronary events (RR 0.84, 95% CI = 0.52-1.35, $P = 0.48$). The risk of vascular death was significantly increased with coxibs and diclofenac (RR 1.58, 99% CI = 1.00-2.49, $P = 0.010$ for coxibs and RR 1.65, 95% CI = 0.95-2.85, $P < 0.019$ for diclofenac). The risk of vascular death was not significantly increased with ibuprofen (RR 1.90, 95% CI = 0.56-6.41, $P = 0.17$) or naproxen (RR 1.08, 95% CI = 0.48-2.47, $P = 0.80$). The risk of hospitalizations related to heart failure was approximately doubled by all NSAIDs (RR 2.28, 95% CI = 1.62-3.20, $P < 0.001$ for coxibs; 1.85, 95% CI = 1.17-2.94, $P < 0.009$ for diclofenac; RR 2.49, 95% CI = 1.19-5.20, $P < 0.016$ for ibuprofen; and RR 1.87, 95% CI = 1.10-3.16, $P < 0.02$ for naproxen; Table 2).

After many years of research and debate, experts also have a better understanding of the underlying pathophysiology of NSAID-associated cardiovascular risk. Higher levels of COX-2 inhibition combined with lower or incomplete COX-1 inhibition appear to be associated with greater risk of cardiovascular thrombotic events (e.g., MI and stroke).[74] These contrasting effects of COX-1 and COX-2 inhibition can alter the balance of thromboxane A2 and prostacyclin and increase the tendency toward thrombus formation. Thromboxane and prostacyclin are substances with opposite effects. Thromboxane A2 is a vasoconstrictor and stimulator of platelet aggregation. COX-1, synthesized in platelets, mediates the production of thromboxane A2. In contrast, prostacyclin is a potent vasodilator and inhibitor of platelet aggregation, and inhibition of COX-2 in vascular endothelium results in the suppression of prostacyclin.[75,76] Yu et al. (2012) demonstrated that elevated cardiovascular risks occur because coxibs suppress prostacyclin.[75] Selectively removing COX-2 in the vasculature in mice reduced urinary excretion of prostacyclin. This depletion predisposed the mice to hypertension and thrombosis, as evidenced by increased platelet reactivity and reduced endothelial nitric oxide synthase (eNOS) expression and subsequent nitric oxide (NO) synthesis, a pivotal cardioprotective molecule. Other less well-understood theories of NSAID-associated cardiovascular toxicity include the COX-2-mediated stimulation of angiogenesis (cardiac collateralization) as well as intracellular "stress-priming" of the cardiac myocytes via ATP-ase pathways.[77,78] These possible mechanisms, in addition to the disequilibrium of the thromboxane A2-prostacyclin balance, create a physiologic state leading to the cardiovascular toxicity of these agents.

Renal Adverse Effects. Recent research has revealed that people with moderate-to-severe kidney disease are likely to use NSAIDs without knowledge of their potential nephrotoxicity.[79] Both traditional NSAIDs and coxibs have been shown to cause adverse renal effects, particularly at high doses.[32,80,81] Various forms of renal complications have been reported, including electrolyte disorders, acute kidney injury, acute interstitial nephritis with or without nephritic syndrome, and papillary necrosis. Risk factors for kidney damage associated with NSAIDs include age greater than 60 years, diabetes, hypertension, heart failure, renal artery stenosis, hypovolemia, and a family history of chronic kidney disease or kidney failure. These adverse effects are attributed to the inhibition of prostaglandin synthesis by both COX-1 and COX-2 in the kidney.[82,83] Prostaglandins are potent renal vasodilators that stimulate the release of renin and regulate renal blood flow. Thus, inhibition of prostaglandins increases the risk of acute and chronic renal insufficiency via reduction in glomerular pressure, largely due to relative constriction of the afferent renal arterioles. Prostaglandin E2 and prostacyclin are important prostanoids involved in maintaining renal function. Prostaglandin E2 reduces sodium reabsorption, and inhibition can cause sodium retention, which can result in peripheral edema, increased blood pressure, weight gain, and worsening of heart failure. Prostacyclin increases potassium secretion primarily by stimulating renin secretion. Thus, inhibition of this prostaglandin can lead to hyperkalemia, particularly in those with pre-existing impaired renal function.

Hepatic Adverse Effects. Although the risk of liver damage related to NSAID use is thought to be rare, several reviews have identified NSAIDs as the most common drugs to cause liver injury.[32,84-90] The estimated incidence of NSAID-associated hepatotoxicity is between 3 and 23 per 100,000 patient-years.[87] Risk factors for NSAID-induced hepatotoxicity include

advanced age (older than 50 years), female gender, underlying autoimmune disease, and concomitant use of other hepatotoxic drugs.[90] Piroxicam, sulindac, nimesulide, and diclofenac are associated with highest risk, while ibuprofen is considered to have the most favorable safety profile among NSAIDs.[84,87] Coxibs have also been linked to liver damage; however, celecoxib appears to be associated with a low risk of injury.[91,92] Several NSAIDs, such as oral bromfenac and lumiracoxib, were withdrawn or never approved in the United States because of hepatotoxicity concerns.[92,93] The mechanism for liver injury is not clearly known, although it appears to be immunologically mediated and idiosyncratic.[86]

Guidelines for the Appropriate Use of NSAIDs: Balancing Risk Versus Benefit

Professional organizations, including the American Academy of Orthopaedic Surgeons (AAOS), American College of Rheumatology (ACR), American Geriatrics Society (AGS), Osteoarthritis Research Society International (OARSI), National Institute for Health and Clinical Excellence (NICE), and European League Against Rheumatism (EULAR), have updated their guidelines to include the proper use of oral and topical NSAIDs and strategies for prevention of side effects; however, the recommendations vary.[23,38,40,41,94-97] For example, the ACR and AAOS support the use of topical or oral NSAIDs as an effective option for the initial management of knee or hand osteoarthritis, along with other treatments such as acetaminophen and tramadol.[23,40] In the guidelines by NICE, oral NSAIDs and coxibs are only regarded as adjunctive treatments.[96] Topical NSAIDs are recommended as first-line therapy. OARSI, on the other hand, suggests using topical NSAIDs as an adjunct or alternative to oral NSAIDs.[95]

Individual organizations have also had different responses and approaches to treatment in view of safety concerns.[98] For instance, in 2005, the American Heart Association (AHA) published guidelines for NSAID use in patients with pre-existing cardiovascular disease or at risk for cardiovascular disease and revised them in 2007.[98] In the revision, a stepwise approach to pain management was provided. Acetaminophen, aspirin, and short-term use of narcotic analgesics are recommended as first-line therapy before using an NSAID. For patients with or at risk for cardiovascular disease, the recommendation is to use a traditional NSAID over highly selective NSAIDs.

Guidelines for the Prevention of NSAID-Associated Risks

To make effective treatment decisions involving NSAIDs, clinicians must balance their benefits and risks.[53,99,100] The appropriate use of NSAIDs involves tailoring treatment to the individual's gastrointestinal and cardiovascular risk profile. In 2009, the American College of Gastroenterology (ACG) issued guidelines for the prevention of NSAID-related ulcer complications and strategies for balancing gastrointestinal and cardiovascular benefits and risks.[53]

Strategies to Reduce Gastrointestinal Risk. Two strategies were described in the ACG guidelines for preventing gastric mucosal damage in chronic NSAID users: (1) coadministration of gastroprotective agents such as misoprostol or proton pump inhibitors (PPIs) or (2) substituting a traditional NSAID with a coxib.[53] In order to determine the appropriate strategy, clinicians must assess the patient's risk factors.[53,99,100] Risk factors for NSAID-related gastrointestinal toxicity include history of peptic ulcer disease or UGIB; advanced age (65 years or older); the presence of comorbidities such as rheumatoid arthritis; and concomitant use of anticoagulants, aspirin, or corticosteroids.[53,101-03] The use of 2 or more NSAIDs at a time places patients at higher risk for developing gastrointestinal problems.[103] *Helicobacter pylori* infection is considered an independent risk factor. Eradication of the infection before starting long-term therapy with an NSAID and routine testing are recommended.

PPIs are typically prescribed and generally considered the preferred cotreatment for the prevention of NSAID-induced gastric and duodenal ulcers; however, recent information regarding their long-term effects has led to questions and concerns regarding their safety.[104-07] These acid-suppressive medications have been linked to cardiac damage, fracture, *Clostridium difficile* infection, increased risk of pneumonia, and nutritional deficiencies (B12 and magnesium) that increase the risk of arrhythmias, seizures, and muscle spasms. With evidence mounting, clinicians are encouraged to factor into their clinical decision making the long-term potential for harm associated with PPIs and possible interactions with other agents.[104]

Balancing Gastrointestinal and Cardiovascular Risks. The ACG guidelines recommend tailoring treatment to the individual patient using risk stratification.[53] This approach involves assessing the patient and identifying not only gastrointestinal risk factors but also cardiovascular risk factors. Patients can be classified into high, moderate, or low risk of NSAID-induced gastrointestinal toxicity. Patients with more than 2 risk factors (advanced age of 65 years or older; use of high-dose NSAID therapy; history of uncomplicated ulcer; or concomitant use of anticoagulants, aspirin, or corticosteroids) plus a history of previously complicated ulcers are considered high risk. The use of traditional NSAID therapy is not recommended for these patients. Instead, a coxib in conjunction with a PPI or misoprostol is suggested. Patients with high gastrointestinal risk and high cardiovascular risk should avoid traditional NSAIDs and coxibs. An alternative therapy should be used. Moderate-risk patients, with 1 or 2 risk factors, are advised to use an NSAID with a PPI or misoprostol. Patients with low or moderate gastrointestinal risk but high cardiovascular risk are advised to use naproxen plus a PPI or misoprostol. Patients with no risk factors are considered to be at low risk, and gastroprotective therapy is not warranted for them. These patients may be treated with a traditional NSAID alone, although recent data suggest that even average-risk NSAID users may also be at risk (Table 3).[108]

TABLE 3 Balancing the Risks: Use of NSAIDs in Patients with Gastrointestinal and Cardiovascular Risks

		Gastrointestinal Risk		
		Low	**Moderate 1-2 Risk Factors**	**High 2 Risk Factors**
Cardiovascular Risk	**Low** (does not require aspirin)	Traditional NSAID alone	Traditional NSAID + gastroprotective agent[a]	Consider alternative non-NSAID therapy or Coxib + gastroprotective agent[a]
	High (requires aspirin)	Naproxen + gastroprotective agent	Naproxen + gastroprotective agent	Alternative non-NSAID therapy

Source: Lanza FL, Chan FK, Quigley EM; Practice Parameters Committee of the American College of Gastroenterology. Guidelines for prevention of NSAID-related ulcer complications.[53]

[a]PPI or misoprostol as gastroprotective agent. H. pylori is considered an independent risk factor and should be treated separately.

coxib = cyclooxygenease-2 (COX-2) inhibitor; NSAIDs = nonsteroidal anti-inflammatory drugs; PPI = proton pump inhibitor.

Barriers to Treatment

The risks associated with NSAID use are a public health issue.[109] A lack of awareness and adherence contribute to the barriers to optimal care and management with NSAIDs.[31,110-13] Studies show that these analgesics are being inappropriately used and prescribed.[114] Preventive strategies are either underutilized or not followed.[115-21] Compounding matters, patients often self-treat with nonprescription NSAIDs, and misuse can lead to a range of complications.

New data show a continued high prevalence of NSAIDs being prescribed to patients at risk for heart disease.[114] In addition, less than half of American adults who take NSAIDs daily report using a gastroprotective agent, indicating that preventive strategies for drug-induced complications are underutilized. In patients who have been prescribed gastroprotective agents, only two thirds who are at high risk for gastrointestinal bleeding continue to be prescribed a PPI after 2 years.[117] Dominant themes seen among physicians' barriers to adherence to NSAID guidelines relate to knowledge, perception, and experience. Specific barriers identified include lack of awareness of the guidelines, distrust in the validity of the guidelines, usability issues of guidelines for special populations, failure to deviate from practice patterns (clinical inertia), individual experiences, and medical heuristics ("rules of thumb").[118] Researchers stressthe need for new guidelines to assist physicians in safe prescribing of NSAIDs and measures for improving concordance.[114,118]

According to a recent survey, a large number of patients report not having received counseling about risks of NSAIDs from either a physician or a pharmacist.[113] Unbeknownst to the clinician, patients may engage in independent self-care with nonprescription NSAIDs but may not know about the potential harms, particularly with multiple NSAID use.[31,110-13] Further complicating matters, NSAIDs are being used unnecessarily. Self-administration of NSAIDs before and during training or competition has become popular among athletes trying to improve performance by preventing pain and inflammation.[122-24] Recent data indicate that the use of these analgesics is not effective in reducing pain and improving performance in endurance athletes. Moreover, NSAIDs are associated with an increased incidence of gastrointestinal, renal, and cardiovascular adverse effects.[125] Concerns have been raised regarding the lack of awareness and education among athletes of the potential harmful effects.

Cost-Effectiveness Considerations

Chronic pain affects millions of Americans.[1,8,9] NSAIDs are the mainstay treatment for managing pain and

Clinical Commentary 1

The withdrawal of refecoxib brought to the attention of clinicians the concerns regarding all NSAIDs, not just COX-2 inhibitors. We had to examine the commonly accepted practice at that time of continuous use of NSAIDs for maintenance therapy. Data became available indicating complications and adverse health events not only involving the gastrointestinal and renal systems but cardiac and cardiovascular events. We now know that using lower doses of NSAIDs for a shorter duration is most appropriate. This is especially true in chronic conditions because there is little inflammation present, and the NSAIDs are primarily being used as a mild analgesic and not for their anti-inflammatory effects. At the same time practitioners were learning to reduce the use of routine NSAIDs, it became more acceptable to regularly prescribe more potent analgesics such as the opioids. This allowed for many patients to be treated without systemic NSAIDs. Now that there are concerns and problems with the continuous use of opioids, there is a renewed interest in finding new forms of NSAIDs that will have less toxicity than the current forms of NSAIDs or opioids.

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inflammation for musculoskeletal pain conditions.[5,30] They can range in cost from $4 to more than $300 per month. Moreover, the side effects associated with NSAID use can impose significant financial burden.[4,126,127] In the United States, the estimated direct medical cost associated with hospital care of UGIB is more than $2.5 billion annually.[126] Despite the availability of inexpensive NSAID treatment options, this potential financial benefit may be offset by the cost associated with preventing or treating NSAID-related complications.[128,129]

Numerous studies have compared the safety, effectiveness, and cost of competing strategies regarding celecoxib versus traditional NSAIDs alone or in combination with gastroprotective agents. Studies confirm the efficacy of gastroprotective agents such as PPIs in preventing NSAID-induced gastrointestinal complications.[130] Across different geographies, most economic models comparing traditional NSAIDs and coxibs have demonstrated that the use of a traditional NSAID plus a gastroprotective agent is the most cost-effective option. Some analyses, however, suggest that coxibs are associated with lower medical care costs.[129-34] Naproxen may be a cost-effective treatment compared with other traditional NSAIDs and coxibs, particularly in patients at high risk.[135,136] When taking into account the overall costs, benefits, and risks, newly approved topical NSAIDs and combination formulations (containing an NSAID and a gastroprotective agent) may be cost-effective over the long term; however, these regimens have not been well established.

Economic evaluations of the cost-effectiveness of coxibs have produced conflicting results. Early economic models found coxibs to be cost-effective, on the basis of less gastrointestinal complications and reduced coprescription with a gastroprotective agent, while others reported a limited safety advantage and higher costs associated with coxibs.[137-40] More recent clinical and economic data have provided better insight into key considerations pertaining to risks, benefits, and cost. Incremental cost per quality-adjusted life-year (QALY) gained appears to vary with individual drugs between studies due to different patient risk categories, varied choices of NSAID comparators, and whether or not the NSAID was combined with a gastroprotective agent.[137] Most evaluations have arrived at similar conclusions, suggesting that coxibs should be reserved for patients at high risk for developing a serious gastrointestinal complication.[128,133] Economic models indicate a gastroprotective agent should be given with traditional NSAIDs and coxibs.[129,141]

In efforts to control costs, managed care organizations and Medicaid programs have implemented utilization management strategies, such as tier placement, prior authorization, and step therapy to restrict the use of celecoxib.[142-44] Studies have shown that these tools effectively reduce utilization and expenditures for the drug, but whether these restrictions confer positive health outcomes and lower costs is not clear. In a comparison study in Medicare patients with arthritis, health plans with celecoxib formulary restrictions were associated with a higher incidence of serious gastrointestinal complications and associated medical costs versus plans without such restrictions.[142]

Results from pharmacoeconomic evaluations have varied, likely due, in part, to different sources of data, different types of studies, or varied treatment comparisons. They may have been conducted in other countries with different drug prices. Results from cost-effectiveness studies should be interpreted carefully, especially as more generic agents become available, and new evidence and interventions emerge.

Clinical Commentary 2

The term "analgesia" refers not just to the relief of pain, but to the balance of pain relief and adverse effects from the medications prescribed. With our increased understanding of pain and its treatment, signals of significant problems with the most currently used analgesics have also become evident. Once the most commonly prescribed analgesics, NSAIDs are now frequently avoided for those with chronic noncancer pain due to clinician concern for potentially fatal upper gastrointestinal bleeding and severe cardiovascular events. The repudiation of these agents has left clinicians with a lack of treatment options, and many have lowered their threshold for considering opioids as a long-term treatment strategy. Potentially, the concerns with NSAID safety have played a role in the increased prescribing of opioids for those with pain who fail other modalities. Recent data suggest that deaths due to prescription opioid overdose have surpassed those due to motor vehicle accidents in many states. Those clinicians in primary or emergency care settings can certainly attest to the high use of health care resources that results from inadequately managed pain.

Given that acetaminophen as monotherapy often does not provide the level of analgesia required by many patients, a safer treatment option than opioids would be ideal when traditional NSAIDs are contraindicated. Novel formulations of NSAIDs with which we already have clinical experience are certainly of interest. We have seen improved tolerability of the topical NSAID products in use today, largely owing to the decreased systemic exposure. However, some pain syndromes do not respond to topical treatment. Newer formulations of NSAIDs that possess similar efficacy to their traditional counterparts, with reduced risk of significant gastrointestinal and cardiovascular effects, would be ideal and would again add the class of NSAIDs back into the treatment armamentarium of clinicians treating chronic mild-to-moderate pain.

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TABLE 4 New and Emerging NSAID Formulations

Drug Candidate	Product Candidate	Type	Target Indication (Pain)	Phase of Development	Key Findings
Diclofenac	Zorvolex	Nanoformulation	Acute Osteoarthritis	Phase 3 (complete) FDA-approved for mild-to-moderate acute pain (October 2013)	Generally well tolerated
Indomethacin	Tiforbex	Nanoformulation	Acute	Phase 3 (complete)	Generally well tolerated
Meloxicam		Nanoformulation	Osteoarthritis	Phase 3 (ongoing)	Phase 3 study in osteoarthritis pain is ongoing
Naproxcinod		CINOD	Osteoarthritis	Phase 3 (complete)	Improved pain and function Upper GI side effects more common with naproxcinod Blood pressure-lowering effects similar to placebo
Naproxen		Nanoformulation	Osteoarthritis	Phase 2 (complete)	Greater total pain relief during 0-12 hours compared with placebo in patients following removal of molars Generally well tolerated
Celecoxib		Nanoformulation		Preclinical	
Ibuprofen		Nanoformulation		Preclinical	
ACS 15 (diclofenac)		H_2S-releasing hybrid		Preclinical	
ATB-337 (naproxen)		H_2S-releasing hybrid		Preclinical	

CINOD = cyclooxygenase inhibiting nitric oxide donator; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; H_2S = hydrogen sulfide; NSAIDs = nonsteroidal anti-inflammatory drugs.

The Future of Pain Relief: New and Emerging NSAID Formulations

Despite the known risks associated with NSAIDs, a recent study reported that primary care physicians largely prefer them for the treatment of chronic pain.[5] Despite their known harms, NSAIDs are the most commonly prescribed drug class, with drug use rates as high as 99%. The FDA and European Medicines Agency (EMA) issued directives to use the lowest effective dose for the shortest duration in order to achieve pain relief and reduce the risk of adverse effects. In response, drug manufacturers have taken action to develop innovative therapeutic products that maintain efficacy but improve patient safety.[145,146]

Doing More with Less—Submicron and Nanotechnology

Nanotechnology has been applied to existing NSAIDs to improve their pharmacodynamic and pharmacokinetic properties.[147-54] A novel platform that uses the process of dry milling reduces the drug particle size to approximately 10 times smaller than the original size.[145] Reformulating NSAIDs using this technology has been found to enhance drug dissolution in the body; however, the impact on long-term safety has not yet been determined.[148,149] On October 18, 2013, the FDA approved the first nanoformulated NSAID, diclofenac, for the treatment of mild-to-moderate acute pain in adults, at 2 different dosage strengths (18 mg and 35 mg).[155] The agency has also accepted for review a New Drug Application (NDA) for indomethacin (Table 4). Several other submicron NSAID products are in development including naproxen, meloxicam, celecoxib, and ibuprofen.

Optimizing Pharmacodynamic-Pharmacokinetic Parameters. A critical problem with NSAIDs is their low solubility, which results in low dissolution rates and consequently poor absorption and bioavailability.[150-54] Altering materials into nanosized dimensions changes the physical properties that govern the pharmacokinetic processes of the drug. Poorly water-soluble drugs such as NSAIDs can thus be rendered more soluble via particle size reduction. The smaller particle size results in an increase in surface-area-to-volume ratio. A higher surface area can thus increase the dissolution rate and consequently improve oral bioavailability and enhance absorption.[150-54] As a result, compared with conventional NSAID formulations, nanoformulated products facilitate a shorter duration to effective blood levels and faster onset of pain relief.

Pharmacokinetic analysis has revealed that nanoformulated indomethacin (20 mg or higher) and diclofenac (18 mg or higher) are absorbed faster than their conventional drug counterpart.[148,149] Under fasting conditions, the time to achieve peak plasma concentrations (Tmax) was 1.11 ± 0.55 hour and 1.25 ± 0.60 hour with 20 mg and 40 mg indomethacin nanoformulations, respectively, and 1.97 ± 0.81 hour with standard oral 50 mg indomethacin.[149] Similarly, the Tmax for 18 mg and 35 mg nanoformulated diclofenac was 0.62 ± 0.35 hour and 0.59 ± 0.20 hour, respectively, versus 0.80 ± 0.50 hour with standard 50 mg diclofenac.[148] In the presence of food, the area

under the concentration-time (AUC) for nanoformulated indomethacin 40 mg was reduced by 26%.[149] Peak concentrations (Cmax) of nanoformulated indomethacin 40 mg were slightly lower compared with conventional indomethacin 50 mg (1,360 ± 424 nanograms per milliliter [ng/mL] vs. 1,408 ± 469 ng/mL, respectively). For nanoformulated diclofenac, the AUC was reduced by 19% in the presence of food.[148] For both indomethacin and diclofenac, the elimination half-lives (t1/2) of the nanoformulations and the standard drug were reported as "similar."[148,149]

In Phase 3 trials, these nanoformulations provided meaningful pain relief within 30 minutes of administration.[156-58] Nanoformulated diclofenac 18 mg and 35 mg maintained significant pain relief for up to 7 hours.

Efficacy. Phase 3 testing of nanoformulated diclofenac and indomethacin has been completed and is ongoing for meloxicam. Recent findings suggest nanoformulated indomethacin and diclofenac are effective in treating acute pain in adults, and nanoformulated diclofenac shows promise for chronic pain.[156-59] Both of these submicron formulations met primary endpoints in Phase 3 trials of providing significant pain relief compared with placebo and were generally well tolerated. As reviewed below, the efficacy data from studies on nanoformulated diclofenac support the approval and indication for use in mild-to-moderate acute pain.

Two randomized, double-blind Phase 3 trials were conducted to assess submicron indomethacin in acute pain.[157,158] In 1 study, adult patients (N = 462) with moderate-to-severe pain following bunionectomy surgery were given 1 of 5 single-day regimens: submicron indomethacin 40 mg 2 times daily; submicron indomethacin 40 mg 3 times daily; submicron indomethacin 20 mg 3 times daily; celecoxib 200 mg 2 times daily with a 400 mg loading dose; or placebo.[157,158] All 3 different dosing regimens of submicron indomethacin demonstrated significant analgesic treatment effects, greater than that of placebo ($P < 0.046$). Over the 48-hour primary study period, patients receiving submicron indomethacin 40 mg 3 times daily experienced the most significant reductions in overall pain intensity, compared with those receiving placebo ($P < 0.001$). Celecoxib demonstrated analgesic efficacy but was not significantly more effective than placebo ($P = 0.103$). Assessments were made at different time points. All 3 indomethacin regimens provided pain relief at 8 and 24 hours, with evidence of analgesia as early as 30 minutes postdose. Indomethacin 40 mg 2 and 3 times daily were statistically superior to placebo in providing pain control over 4 hours after study entry ($P = 0.014$ and $P = 0.013$, respectively). The second study evaluating submicron indomethacin in acute pain had a similar framework (with the exception of the celecoxib arm), enrolling 373 adults.[158] Submicron indomethacin 40 mg 3 and 2 times daily were associated with significant analgesic efficacy compared with placebo ($P = 0.034$ and $P = 0.023$, respectively). The difference between submicron indomethacin 20 mg 3 times daily and placebo was not statistically significant ($P = 0.680$).

A randomized, double-blind Phase 3 trial was also conducted on submicron diclofenac in patients with acute pain following elective bunionectomy surgery.[156] Participants received oral doses of submicron diclofenac (35 mg 3 times daily and 18 mg 3 times daily); celecoxib (200 mg 2 times daily, 400 mg loading dose); or placebo. Both doses of submicron diclofenac and celecoxib were associated with significant pain control compared with placebo ($P < 0.001$, $P = 0.010$, and $P = 0.011$, respectively). Pain relief scores over 48 hours were numerically higher with the 35 mg diclofenac dose than the 18 mg dose.

Submicron diclofenac was also assessed in patients with chronic pain.[159] In a randomized, double-blind, Phase 3 trial, adult patients (N = 305) aged 41-90 years with osteoarthritis of the hip or knee received either submicron diclofenac 35 mg 3 times daily, submicron diclofenac 35 mg twice daily, or placebo.[159] Submicron diclofenac 35 mg 3 times daily demonstrated significant improvements in the treatment of osteoarthritis pain compared with placebo, as measured by the change from baseline to week 12 on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; $P < 0.002$). Although WOMAC scores improved with the twice daily dose, submicron diclofenac 35 mg twice daily failed to separate statistically from placebo ($P < 0.08$).

Safety. Safety data from a 12-week Phase 3 trial assessing submicron diclofenac in patients with osteoarthritis, presented at the ACR annual meeting in October 2013, revealed no serious gastrointestinal, cardiovascular, or renal adverse events.[160] Overall, the adverse events were generally mild and similar across the placebo and 2 treatment groups (submicron diclofenac 35 mg 2 and 3 times daily). The most common adverse reactions (occurring in less than 10% in any treatment group) were nausea, diarrhea, headache, constipation, upper respiratory infection, upper abdominal pain, nasopharyngitis, sinusitis, serum creatinine elevation, dyspepsia, ALT elevation, and urinary tract infection. Despite the promising safety data, the recently approved nanoformulated diclofenac will be required to carry a black box warning highlighting the potential of long-term harm. Similar to the labeling on conventional NSAIDs, the warning for the new formulation will state the increased risk for cardiovascular and gastrointestinal events.[155] Safety data for submicron indomethacin in patients with acute pain were also presented at the 2013 ACR meeting.[161] Combined safety data from 2 Phase 3 trials showed no cases of severe gastrointestinal, cardiovascular, or renal adverse events. Adverse events were similar across all treatment groups. The most common adverse events were nausea, postprocedural edema, headache, dizziness, vomiting, postprocedural hemorrhage, and constipation.

Multitarget Drugs

Cyclooxygenase-inhibiting NO donors (CINODs or NO-NSAIDs) represent a new class of drugs in development that target multiple pathways, including COX inhibition and

NO donation.[162] NO is a potent vasodilator with known protective effects on the gastrointestinal tract.[163] It serves to protect the integrity of the gastrointestinal mucosa by stimulating the secretion of mucus and bicarbonate, inhibiting leukocyte endothelial cell adhesion, protecting epithelial cells against injury, and down-regulating the release of inflammatory mediators. The novel multitarget approach combines the gastrosparing and antihypertensive effects of NO with the anti-inflammatory properties of NSAIDs. Naproxcinod was the first CINOD developed and investigated in well-designed clinical trials; however, it was rejected by the FDA because of a lack of long-term data.[162] Development of naproxcinod is currently suspended and awaiting further research funding.[164]

Efficacy

Three Phase 3 studies and 1 long-term safety extension study have been conducted to evaluate the efficacy of naproxcinod for the treatment of signs and symptoms of osteoarthritis of the knee and hip.[165-68] In these randomized, double-blind, placebo-controlled trials, naproxcinod 750 mg twice daily and 375 mg twice daily were compared with naproxen 500 mg twice daily and placebo. The primary endpoints were WOMAC pain and function subscale scores and patient overall rating of disease status. All 3 studies demonstrated similar results. Naproxcinod 750 mg twice daily and 375 mg twice daily significantly improved WOMAC pain and function subscale scores from baseline to week 13 and were superior to placebo for all 3 endpoints. The researchers stated that the efficacy of naproxcinod was similar to that of naproxen. However, the FDA determined, using a noninferiority margin of 70% of the treatment effect size, that the evidence did not support similar efficacy.[169]

Safety

Based on Phase 3 data, naproxcinod is generally well tolerated for over 1 year with blood pressure effects similar to placebo and less systolic elevation than that associated with naproxen.[165-68] Upper gastrointestinal-related side effects (e.g., constipation, diarrhea, dyspepsia, nausea, or upper abdominal pain) were more frequently reported with naproxcinod compared with placebo and naproxen. Per the FDA review, the safety profile of naproxcinod was found to be similar to other NSAIDs.[169]

Hydrogen Sulfide-Releasing (H_2S) Drugs

Another class of hybrid drugs, bearing hydrogen sulfide-releasing (H_2S) moieties, is being designed to enhance gastrointestinal and cardiovascular safety.[170] H_2S is an endogenous gaseous mediator shown to modulate inflammatory processes and exert vasodilatory activity.[171] The mechanism being explored to reduce toxicity involves the release of hydrogen sulfide and enhanced antioxidant activity.[170] Early research from animal studies suggests these compounds (such as ACS 15 [diclofenac derivative] and ATB-337 [naproxen derivative]) produce anti-inflammatory activity and are associated with lower gastrointestinal and cardiovascular toxicity.[172-75] Currently, these compounds in development are in preclinical stages.

Conclusions

Musculoskeletal-related disorders are a leading cause of disability worldwide.[1] In the United States, these painful conditions affect nearly half of the population and are the most common reason for patients to visit their primary care physicians. NSAIDs are among the most commonly used medications for musculoskeletal conditions. However, the safety of these analgesics garnered attention after evidence of harm emerged. After the benefits of selective COX-2 inhibition were challenged, the focus of research went towards safety and understanding the risks associated with all NSAID regimens.

Over the last decade, new light has been shed on NSAIDs, and recent evidence has renewed interest. Current research shows that both traditional NSAIDs and coxibs increase the risk of gastrointestinal and cardiovascular toxicity, but with proper risk assessment these dangers can be predicted. Novel approaches aim to utilize these drugs with known efficacy for pain while reducing the risk of toxicity. With new data to help guide decision making and the anticipated increase in pharmacological options for managing musculoskeletal pain, the role of the managed care professional is particularly important in this evolving field.

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