Supplement to

CLINICIAN®

Vol. 23 No.10 August 2005

Presented by:
The US Department of Health and Human Services Office on Women's Health

In cooperation with:
American Pharmacists Association
American Academy of Nurse Practitioners
American Academy of Physician Assistants

Sponsorship provided by:
University of Colorado School of Medicine

Supported by an educational grant from:
McNeil Consumer & Specialty Pharmaceuticals

State-of-the-Art Management of Mild-to-Moderate Pain

Multimodal Management of Mild-to-Moderate Osteoarthritis, Musculoskeletal Pain, and Other Conditions

DISCLOSURES OF COMMERCIAL INTEREST

The University of Colorado School of Medicine, as a sponsor accredited by the Accreditation Council for Continuing Medical Education, must ensure balance, independence, objectivity, and scientific rigor in all its sponsored educational activities. All faculty participating in a sponsored activity are expected to disclose to the activity audience any significant financial interest or other relationship with (1) manufacturers of any commercial products and/or providers of commercial services discussed in an educational presentation and (2) any commercial supporters of the activity. Disclosure of a relationship is not intended to suggest or condone bias, but is made to provide participants with information that might be of potential importance to their evaluation of the material presented in this supplement.

THE FOLLOWING FACULTY HAVE AFFILIATIONS WITH ONE OR MORE OF THE CORPORATE ORGANIZATIONS INVOLVED WITH PRODUCTS TO WHICH THEIR PRESENTATIONS WILL REFER IN THIS CME ACTIVITY:

Arnold P. Advincula, MD, has no financial relationships to disclose.

Louis C. Almekinders, MD, has received grants/research support from McNeil Consumer & Specialty Pharmaceuticals.

Gordon D. Benson, MD, is a consultant for McNeil Consumer & Specialty Pharmaceuticals.

Klea D. Bertakis, MD, MPH, has received grants/research support from the Agency for Healthcare Research and Quality.

Daniel O. Clegg, MD, has received grants/research support from Abbott Laboratories, Amgen Inc., Bristol-Myers Squibb Company, GlaxoSmithKline, Glenwood, LLC, IDEC Pharmaceuticals Corporation, MedImmune, Inc., Merck & Co., Inc., and XOMA, LLC, to conduct research trials on their behalf. Dr. Clegg is also a consultant/scientific advisor for Amgen, Inc., Centocor, Inc., McNeil Consumer & Specialty Pharmaceuticals and Wyeth Pharmaceuticals.

Byron Cryer, MD, is a consultant for AstraZeneca Inc, McNeil Consumer & Specialty Pharmaceuticals, Merck & Co., Inc., and TAP Pharmaceuticals Inc. Dr. Cryer is a member of the speakers bureau for Merck & Co., Inc., Pfizer Inc, and TAP Pharmaceuticals Inc. He has received research grants from Merck & Co., Inc., TAP Pharmaceuticals Inc, and Wyeth Pharmaceuticals.

Richard C. Dart, MD, PhD, has received grants/research support from and is a consultant for McNeil Consumer & Specialty Pharmaceuticals.

Kathleen B. Digre, MD, has received grants/research support from GlaxoSmithKline, Merck & Co., Inc., and Pfizer Inc. Dr. Digre is a consultant for AstraZeneca Inc, GlaxoSmithKline, and Ortho-McNeil Pharmaceutical, Inc. She is a member of the speakers bureau for AstraZeneca Inc, GlaxoSmithKline, Merck & Co., Inc., Ortho-McNeil Pharmaceutical, Inc., and UCB Pharma.

Janet P. Engle, PharmD, FAPhA, is a consultant for Procter & Gamble and Schering-Plough.

A. Mark Fendrick, MD, is a consultant and speaker for AstraZeneca Inc, McNeil Consumer & Specialty Pharmaceuticals, Merck & Co., Inc., Procter & Gamble, and TAP Pharmaceuticals Inc.

Roger B. Fillingim, PhD, has no financial relationships to disclose.

J. Michael Gaziano, MD, MPH, has received grants/research support from McNeil Consumer & Specialty Pharmaceuticals, Merck & Co., Inc., and Wyeth Pharmaceuticals. Dr. Gaziano is a consultant for McNeil Consumer & Specialty Pharmaceuticals.

Deborah S. Litman, MD, FACR, is a consultant for McNeil Consumer & Specialty Pharmaceuticals. Dr. Litman is a member of the speakers bureau for Merck & Co., Inc., and Ortho-McNeil Pharmaceutical, Inc.

Kate Lorig, RN, DrPH, receives royalties from Perseus Publications for the Arthritis Helpbook.

Wayne A. Ray, PhD, is a consultant for Pfizer Inc.

Steven Stovitz, MD, CAQSM, has no financial relationships to disclose.

Cheryl Wright, MD, is a member of the speakers bureau for McNeil Consumer & Specialty Pharmaceuticals.

DISCLAIMER

State-of-the-Art Management of Mild-to-Moderate Pain: Multimodal Management of Mild-to-Moderate Osteoarthritis, Musculoskeletal Pain, and Other Conditions is a certified continuing education activity providing an in-depth, expert review and analysis of recent scientific advances and clinical controversies in the management of mild-to-moderate pain. The views presented are those of the faculty and/or contributing editors and not necessarily those of the producer, commercial supporter, the US Department of Health and Human Services Office on Women's Health, or the University of Colorado School of Medicine. Some information presented in this supplement may be off label. Before using any product discussed in this publication, clinicians should consult the full prescribing information.

State-of-the-Art Management of Mild-to-Moderate Pain: Multimodal Management of Mild-to-Moderate Osteoarthritis, Musculoskeletal Pain, and Other Conditions reports highlights from a roundtable meeting presented by the US Department of Health and Human Services Office on Women's Health, under the auspices of the University of Colorado School of Medicine, and in cooperation with the American Geriatrics Society, the American Pharmacists Association, the American Academy of Nurse Practitioners, and the American Academy of Physician Assistants.

This material is based upon a review of multiple sources of information, but is not exhaustive of the subject matter. Healthcare professionals and other individuals should review and consider other publications and material about the subject and not rely solely upon the information contained within this publication.

Please direct all correspondence to:

Editor, *Clinician*®
SynerMed® Communications
Department MC54G
405 Trimmer Road
PO Box 458
Califon, NJ 07830

This supplement was developed and produced by SynerMed® Communications for the University of Colorado School of Medicine under an educational grant from McNeil Consumer & Specialty Pharmaceuticals.

INTENDED AUDIENCE

Healthcare professionals

LEARNING OBJECTIVES

After reading this *CLINICIAN*® monograph supplement, the healthcare professional should be able to:

- Evaluate psychosocial, socioeconomic, and pharmacoeconomic issues related to mild-to-moderate pain and pain management
- Recognize the impact that gender differences may play on pain perception and perceived effectiveness of therapy
- Recognize the role of age and cognitive function in the perception of pain, ability to communicate with caregivers, and perceived effectiveness of therapy
- Explore issues related to common medical conditions that cause pain
- Educate patients on the safe use of pain medications
- Examine the risks and benefits of commonly used analgesics in the management of mild-to-moderate pain

NEEDS ASSESSMENT

In the United States, approximately $3 billion per year is spent on over-the-counter (OTC) analgesics, including aspirin, other non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. These agents are often used for the relief of osteoarthritis (OA) and mild-to-moderate pain of musculoskeletal injuries. When used correctly, these medications can provide significant relief from pain. Prescription medications are also believed to be effective; however, recent studies have demonstrated that the cyclooxygenase-2 inhibitors have been linked to an increased risk of cardiovascular (CV) events. Although further study is needed to determine the exact relationship between these agents and CV events, many questions have emerged. Further complicating this issue, while many available NSAIDs are effective at relieving pain, these agents have been associated with gastrointestinal (GI) complications such as GI bleeding. Thus, a thorough understanding of non-NSAID analgesics is becoming even more important to clinicians.

Therapeutic interventions have been shown to relieve pain and reduce disability. Optimal therapy for OA and mild-to-moderate pain should be targeted to the individual. Despite the fact that pharmacologic measures are vital to the treatment of OA and mild-to-moderate pain, nonpharmacologic measures, such as exercise, patient education, and weight loss, cannot be overlooked as they are essential to the overall long-term management of these conditions. An understanding of the various physical therapies that can aid in the lessening of pain is critical.

This continuing medical education (CME) activity has been developed to educate healthcare professionals to evaluate the latest safety and efficacy issues regarding oral analgesic treatment strategies, including OTC agents, for the management of OA and mild-to-moderate pain. The importance of nonpharmacologic measures will also be addressed as a cornerstone to the management of this condition.

CME CERTIFICATION

The University of Colorado School of Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Physicians

The University of Colorado School of Medicine designates this educational activity for a maximum of 3.0 category 1 credits toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.

This activity should take approximately 3.0 hours to complete. The participant should, in order, read the learning objectives contained in the supplement, answer the multiple-choice posttest, and complete the Registration/Evaluation Form.

Nurse Practitioners

This program has been approved for 3.0 contact hours of continuing education by the American Academy of Nurse Practitioners. Program ID 0505233.

Physician Assistants

This program has been reviewed and is approved for a maximum of 3.0 hours of AAPA Category I (Preapproved) CME credit by the Physician Assistant Review Panel. Approval is valid for one year from the issue date of August 1, 2005. Participants may submit the self-assessment at any time during that period.

This program was planned in accordance with AAPA's CME Standards for Enduring Material Programs and for Commercial Support of Enduring Material Programs.

Release Date: August 15, 2005

Expiration Date: August 31, 2006

Table of Contents

Page

Please look for the entire US Department of Health and Human Services *State-of-the-Art Management of Mild-to-Moderate Pain* series, which can be found at http://www.medcme.org.

INTRODUCTION

Pain is highly prevalent in the United States and is the most common reason why patients seek advice from their clinicians. Surveys suggest that in the US population, 1 in every 5 people suffers from chronic pain[1] and 1 in every 4 people suffers from musculoskeletal impairments.[2] Pain is the third leading reason for absence from work in the United States and, in the case of chronic pain, results in annual expenditures of at least $50 billion.[1] These numbers are expected to grow exponentially as the population continues to age and develop musculoskeletal disorders.

The pain and disability caused by musculoskeletal impairments are familiar to patients and clinicians who treat them. Patients with pain often experience depression, anxiety, work-related stress, social isolation, and poor social support. Historically, pain has been managed inadequately, in part because it was conceptualized as a normal consequence of illness, aging, and daily life. Within this context, patients often fail to seek medical attention for their pain. In addition, concerns about addiction and adverse events associated with certain pain medications have contributed to insufficient management.

The assessment and treatment of mild-to-moderate pain should be multidimensional. Both pharmacologic and nonpharmacologic therapies are available to treat these conditions, but the success of these approaches varies considerably, and, in many circumstances, the data to support the use of some of these approaches are lacking. Further complicating the situation is the recent withdrawal of rofecoxib and valdecoxib—both cyclooxygenase-2–selective nonsteroidal anti-inflammatory drugs (NSAIDs)—from the market because of their adverse cardiovascular (CV) event profiles. It also has been reported that celecoxib may be associated with negative CV effects.[3] Additionally, the US Food and Drug Administration (FDA) has asked manufacturers of all prescription NSAIDs to revise their labeling to include a boxed warning highlighting the potential for increased risk of CV events and gastrointestinal (GI) bleeding associated with their use. Manufacturers of celecoxib and all other prescription NSAIDs have been asked to revise their labeling to include a Medication Guide for patients to help make them aware of the potential for CV and GI adverse events associated with the use of this class of drugs.

In addition, FDA is asking the manufacturers of all over-the-counter (OTC) NSAIDs to revise their labels to include more specific information about potential CV and GI risks, along with information to assist consumers in the safe use of these drugs. FDA also is asking manufacturers of OTC NSAIDs to include a warning about the risk of potential skin reactions. The labeling of prescription NSAIDs already addresses potential skin reactions.[4]

In an effort to examine the impact of mild-to-moderate pain on individuals, society, and the healthcare system, a group of experts in various aspects of pain management met under the auspices of the Office on Women's Health of the US Department of Health and Human Services to present and discuss information for educational initiatives designed to help improve clinical outcomes. The focus of these deliberations was mild-to-moderate pain—a score of 2 to 6 on a visual analog or numeric rating scale, with 0 representing no pain and 10 representing severe pain. Because musculoskeletal conditions consist of a broad array of diseases and injuries, the faculty focused on inflammation, soft tendon and muscle injuries, osteoarthritis, and low back pain. Two additional areas where pain is commonplace were also addressed: headache and dysmenorrhea. This supplement presents highlights of these discussions.

The goal of this supplement is to provide clinicians with useful information on the pathophysiology, risk factors, clinical features, and disease outcomes of various painful conditions, as well as to provide a comprehensive review of available analgesics, their efficacy, side-effect profiles, and appropriateness of use in different painful conditions.

REFERENCES

1. Katz WA. Musculoskeletal pain and its socioeconomic implications. *Clin Rheumatol.* 2002;21(suppl 1):S2-S4.
2. Medscape Medical News. One of every four Americans has a musculoskeletal condition. Medscape. Available at: www.medscape.com/viewarticle/411950_print. Accessed June 18, 2004.
3. National Institutes of Health. Questions and answers: NIH halts use of COX-2 inhibitor in large cancer prevention trial (press release, December 17, 2004). Available at: http://www.nih.gov/news/pr/dec2004/od-17Q&A.htm. Accessed January 11, 2005.
4. Food and Drug Administration. FDA announces series of changes to the class of marketed non-steroidal anti-inflammatory drugs (NSAIDs). Available at: http://www.fda.gov/bbs/topics/news/2005/NEW01171.html. Accessed April 21, 2005.

MILD-TO-MODERATE PAIN AND ITS MANAGEMENT

Daniel O. Clegg, MD
Professor of Medicine
Division of Rheumatology
University of Utah School of Medicine
Salt Lake City, Utah

Richard C. Dart, MD, PhD
Director, Rocky Mountain Poison and Drug Center, Denver Health
Professor of Surgery (Emergency Medicine)
University of Colorado
Health Sciences Center
Denver, Colorado

Janet P. Engle, PharmD, FAPhA
Associate Dean for Academic Affairs
Clinical Professor of Pharmacy Practice
University of Illinois at Chicago
College of Pharmacy
Chicago, Illinois

A. Mark Fendrick, MD
Professor
Internal Medicine and Health Management and Policy
University of Michigan
Ann Arbor, Michigan

Roger B. Fillingim, PhD
Associate Professor
University of Florida College of Dentistry
Public Health Services and Research
Gainesville, Florida

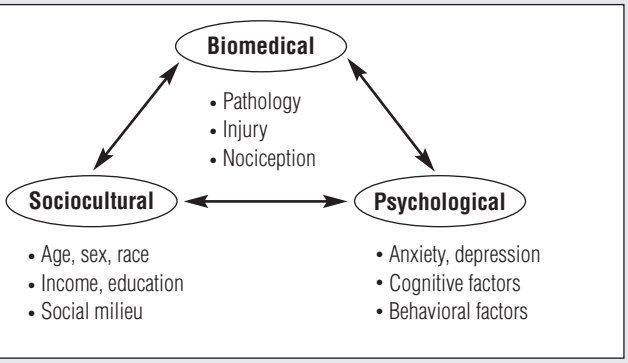
PAIN: A MULTIDIMENSIONAL EXPERIENCE

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.[1,2] Broadly, pain comprises 2 classes—nociceptive and neuropathic pain. Nociceptive pain results from stimulation of nociceptive receptors transmitted over intact neural pathways. This is what we think of as "normal" pain occurring in response to a potentially damaging stimulus. In contrast, neuropathic pain results from damage to neural structures and often may involve neural supersensitivity, exemplified by phantom limb pain.

Pain definitions accommodate a vast number of etiologic factors that may be illustrated in a multidimensional model composed of biomedical, sociocultural, and psychological considerations (Figure 1).[3] The validity of this interactive model is supported by both animal and human studies demonstrating effects of gender, age, ethnicity, and psychological, cognitive, and cultural factors in nociception, as well as in drug responsivity.

Figure 1

A BIOPSYCHOSOCIAL MODEL OF PAIN[3]



Reprinted with permission from Dart RC, Clegg DO. *Clinical Courier*® Vol 22, No. 4. Califon, NJ: SynerMed® Communications; 2004:1-8.

For example, male rats demonstrate a higher pain threshold to mechanical nociception than do females and have greater responsivity to μ-opioid agonists.[4] Clinical data suggest that human females have lower pain thresholds than do males and account for a higher proportion of those with chronic pain conditions.[5-7] The causal basis of the observed differences is unknown, but experimental data provide some interesting clues.

A systematic review of the literature on gender differences in experimental pain perception concluded that women showed lower pain thresholds and tolerances across multiple stimulus modalities, and these gender differences were moderate in magnitude.[5] More recently, in a study that assessed putative gender differences in experimental pressure pain threshold (PPT) in the first dorsal interosseous muscle, investigators found that women exhibited significantly lower mean PPTs than did men (P=.01 for the difference), which were maintained for 14 repeated measures for each subject within a 1-hour period (Figure 2).[6] In another study, painful laser stimulation resulted in different cerebral activation patterns in men and women.[7] Investigators speculated that these differences in pain processing might be important in various clinical conditions, such as migraine, in which prevalence is higher in women.

There are also gender differences in the use of prescription pain medications, which emerge at puberty and continue into adulthood.[8] Although hormonal/developmental factors could account for these differences, puberty also marks a time of expanding differences in culturally influenced sex

roles. There also appear to be gender differences in the effectiveness of analgesics. For example, women showed greater analgesia response to mixed-action opioids after dental surgery.[9] In an experiment that measured electrical pain, men exhibited greater responsivity to ibuprofen than did women,[10] although gender differences in analgesia with ibuprofen were not observed after dental surgery.[11] Numerous other examples of gender differences have been described, suggesting that additional study is needed to clarify potentially important clinical implications of these differences.

Ethnic differences in pain severity, disability, and connotation have been reported in a number of circumstances. Generally, in clinical settings, whites report less pain and fewer pain consequences than do blacks or Hispanics,[12] and blacks have shown greater sensitivity to experimentally induced pain than have whites in laboratory studies.[13] In addition, minorities may be undertreated for pain.[14-16]

Additionally, psychological and cognitive factors can modulate pain perception. The influence of stress on pain can vary depending on the nature and duration of the stressful stimuli and the type of pain involved.[17] Various forms of psychological distress and cognitive expectations can increase the risk of chronic pain, the amount of analgesic used, and the level of pain severity.[18-20]

Consequences of Chronic Pain

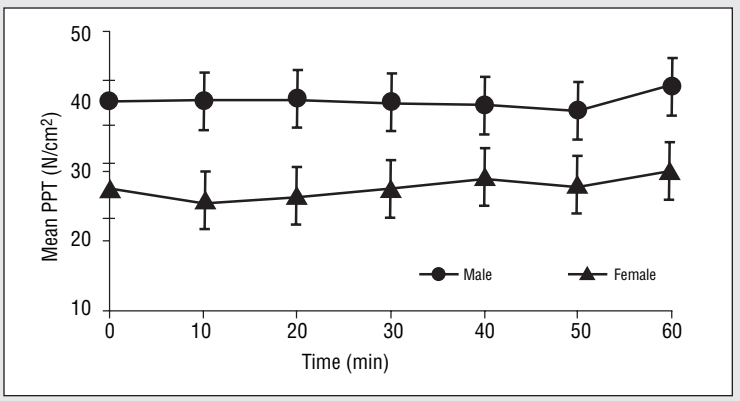
Uncontrolled pain results in substantial socioeconomic burdens. A major contributor to the cost is the utilization of healthcare resources. Yelin and Callahan used the 1990-1992 National Health Interview Survey and a literature review to estimate that healthcare utilization due to all musculoskeletal conditions totaled more than $149 billion.[21] An updated economic burden of musculoskeletal conditions was derived using the 1996 Medical Expenditure Panel Survey, which showed that patients with musculoskeletal conditions were 50% more likely to utilize healthcare services than were those with nonmusculoskeletal chronic conditions.[22]

Furthermore, chronic pain costs employers in the United States an estimated $61 billion annually in lost productivity.[23] According to a cost survey of common pain conditions in the US workforce, headache is the most common pain condition (5.4%) resulting in lost productive time, followed by back pain (3.2%), arthritis pain (2.0%), and other musculoskeletal pain (2.0%). The majority of lost productive time (76.6%) was explained by reduced performance while at work, and not work absence (Table 1).[23] These estimated costs do not include lost productive time costs associated with dental pain, cancer pain, menstrual pain, gastrointestinal (GI) pain, or neuropathy. Elsewhere, it has been estimated that dysmenorrhea is responsible for 600 million hours of absenteeism annually in the United States, with an estimated economic loss of $2 billion.[24]

The cost of caring for patients with arthritis is an even greater burden, which is increased significantly by adverse GI effects associated with nonsteroidal anti-inflammatory drug (NSAID) use in this population. In a study that assessed the direct medical costs of arthritis and side effects resulting from the treatment of the disease, 25% of arthritis patients

Figure 2

GENDER DIFFERENCES IN PRESSURE PAIN THRESHOLD (PPT)[6]



Line graph of mean PPT (N/cm^2) for each gender group with repeated measures at 10-minute intervals over 1 hour. Mean PPT for group (n=30) and mean of 2 PPT readings taken at each time point. Error bars=standard error of the mean.

Adapted with permission from Chesterton LS et al. *Pain.* 2003;101:259-266.

Table 1

TOTAL COST OF LOST PRODUCTIVE TIME DUE TO COMMON PAIN CONDITIONS IN THE US WORKFORCE[23]

	Type of Pain, Cost in Billions of Dollars (SE)				
	Total	Headache	Arthritis	Back	Other*
Total productive time lost	61.3 (2.2)	19.6 (1.0)	10.3 (0.7)	19.8 (1.7)	11.6 (0.9)
Absenteeism	14.4 (1.5)	4.2 (0.6)	1.6 (0.4)	6.0 (1.3)	2.6 (0.3)
At work, but work impaired due to pain	46.9 (1.8)	15.4 (0.7)	8.7 (0.6)	13.8 (1.1)	9.0 (0.8)

SE, standard error.
*Includes unspecified musculoskeletal pain.
Adapted with permission from Stewart WF et al. *JAMA.* 2003;290:2443-2454.

studied were found to have GI side effects resulting from NSAID use, which led them to seek additional medical care.[25] Treatment costs in this study included the cost of treating the disease plus the cost of adverse drug reactions, which totaled $211/quarter year per patient (Table 2).[25] Treatment itself accounted for 69% of total costs, whereas treating adverse GI events accounted for 31%, adding 45.5% to the cost of arthritis treatment. After extrapolating costs to the entire US population with arthritis, a sum of $3.9 billion for GI side effects makes total direct medical costs $12.5 billion annually.[25]

Other consequences of chronic pain may be more difficult to measure—for example, potential alterations in the clinician-patient interaction. Research has shown that clinician practice style is influenced by several demographic factors, including patient gender, age, income, education, presence of depression, and self-reported health status.[26-28] In a recent study, 509 new patients were randomly assigned to visit primary care physicians, and physician practice styles were assessed by videotape. When patients were in pain, physicians spent less time on preventive services and encouraging active participation in care; more time was spent on history taking and the physical examination.[29]

Managing Mild-to-Moderate Pain

Interventions for pain management span an array of modalities, including psychosocial, pharmacologic, and physical—the treatment triad. A key challenge is to integrate and incorporate these options into clinical practice.

Nonpharmacologic Approaches

Nonpharmacologic interventions include patient education, distractions (internal [eg, counting, praying] or external [eg, music, television, listening to someone read]), relaxation/biofeedback, cognitive-behavioral therapy, and hypnosis. The Arthritis Self-Management Program (ASMP), based on the concept of self-efficacy, is one model for the management of mild-to-moderate pain. Self-efficacy has been defined as "people's beliefs about their capabilities to produce designated levels of performance that exercise influence over events that affect their lives. Self-efficacy beliefs determine how people feel, think, motivate themselves and behave."[30] The ASMP provides highly interactive, small-group workshops that are designed to help people gain self-confidence in their ability to control mild-to-moderate pain symptoms and better understand how their health problems affect their lives. In clinical trials, the ASMP has been shown to reduce pain significantly at 4 months, with the improvement being maintained at a 20-month follow-up assessment ($P \leq .05$).[31] (More detailed information about the ASMP can be found at http://patienteducation.stanford.edu/.)

The effectiveness of psychological interventions for pain management has been well documented. A National Institutes of Health Technology Assessment Panel determined that there is strong evidence to support the use of relaxation techniques and hypnosis in reducing chronic pain and moderate evidence to support cognitive-behavioral treatments and biofeedback.[32] For example, preoperative coping imagery reduces pain and cortisol responses following abdominal surgery,[33] whereas hypnosis and relaxation training can reduce experimental and acute clinical pain.[34,35]

Physical Modalities

Thermal and physical therapy, acupuncture, weight loss, and transcutaneous electrical nerve stimulation each have potential roles in the management of mild-to-moderate pain. The evidence basis is limited for some of these methods, but, in general, the concept of multimodal therapy is well supported.[36-38] Ongoing research should continue to shed light on the efficacy, safety, and role of each of these modalities in pain management.

Considerations in Selecting Drug Therapy

Despite the numerous analgesic products on US pharmacy shelves, there are only 5 active analgesic ingredients available over-the-counter (OTC): acetaminophen and the nonselective NSAIDs aspirin, ibuprofen, ketoprofen, and naproxen sodium. These agents play an important role in pain management, but appropriate use can be improved. Consumers often neglect to read product labels and can be poorly informed about safe dosing and administration. When consumers fail to read the labels,

Table 2

TOTAL COST OF CARING FOR PATIENTS WITH ARTHRITIS[25]

	Cost/Quarter per Patient ($)		
Service	Arthritis Treatment	Adverse GI Drug Reactions*	Total
Inpatient hospital	31	25	56
Physician/clinic	36	13	49
Outpatient pharmaceuticals	78	28	106
Total	145	66	211

GI, gastrointestinal.
*Associated with nonsteroidal anti-inflammatory drug use.
Adapted with permission from Bloom BS. *Am J Med.* 1988;84(suppl 2A):20-24.

they unwittingly put themselves at risk of overmedicating, with its attendant adverse consequences.

Each OTC analgesic agent possesses unique properties that affect its suitability for individual patients. Clinicians play an important role in advising patients regarding which agents best meet their needs and in ensuring that OTC analgesics are used appropriately. Careful consideration of patient characteristics (eg, age, condition to be treated, concomitant conditions and therapies) and medication profiles (eg, safety, tolerability, efficacy, mechanism of action, concomitant medications) should guide analgesic choice.

Acetaminophen. Acetaminophen has both analgesic and antipyretic properties and is commonly used to treat fever and pain. Its analgesic mechanism is unknown; however, acetaminophen is believed to increase the pain threshold within the brain.[39] Acetaminophen produces minimal effects on prostaglandin synthesis; however, greater inhibition has been observed in the central nervous system than in the periphery. Its analgesic/antipyretic potency is similar to that of aspirin, but it is devoid of anti-inflammatory effects.

When used at recommended dosages of up to 4000 mg/d, acetaminophen has an excellent safety and efficacy profile and is the most widely used medication for pain and fever.[40] Acetaminophen is efficacious in the treatment of a variety of mild-to-moderate pain states, and it is recommended as first-line therapy in many pain syndromes, including osteoarthritis.[41,42] Acetaminophen has fewer side effects than do NSAIDs, and it is recommended for use when NSAIDs are contraindicated (eg, in elderly patients or patients with asthma, peptic ulcers, or renal insufficiency).[43] There have been reports of serious adverse effects associated with acetaminophen, but these are usually a result of intentional overdose by a suicidal patient[44] (see "Patient Considerations: Special Populations" article, page 20).

Occasionally, unintentional overdose can occur when patients use multiple analgesic products and/or cough and cold preparations that contain acetaminophen, or they exceed recommended dosing guidelines. When used as directed, acetaminophen is generally perceived to be the safest OTC analgesic. Although the majority of consumers use acetaminophen responsibly, patients should be counseled to stay within the recommended dosing guidelines when taking acetaminophen or acetaminophen-containing products.

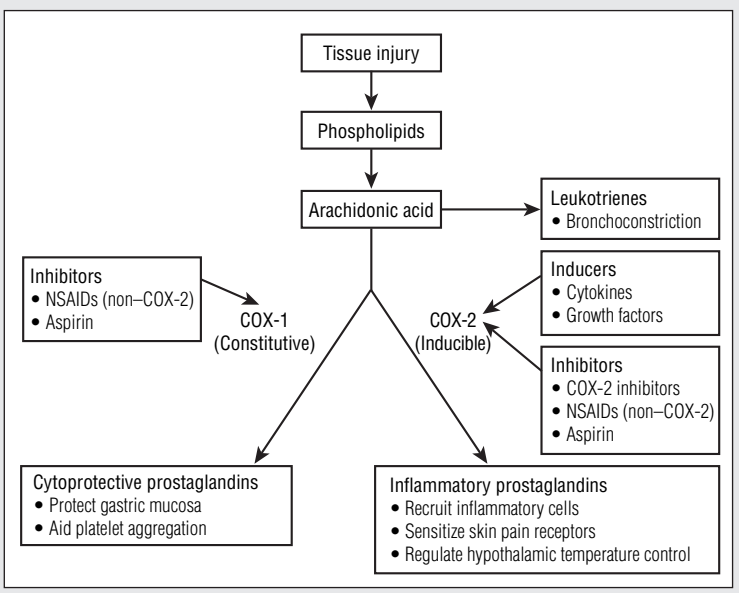
Nonsteroidal Anti-inflammatory Drugs. NSAIDs comprise a broad category of drugs, with each having analgesic, anti-inflammatory, and antipyretic effects. NSAIDs have demonstrated efficacy in the management of fever and mild-to-moderate pain and, at higher doses, inflammation, but NSAIDs are associated with a wide spectrum of adverse GI effects that range from nuisance symptoms, such as dyspepsia, to serious GI complications, such as GI bleeding and ulcers.[45,46] Nuisance symptoms can negatively impact patient adherence. More recently, questions regarding the cardiovascular impact of NSAIDs have arisen and will be reviewed in later sections of this supplement.

It is generally agreed that the principal pharmacologic effect of NSAIDs is their ability to inhibit prostaglandin synthesis by inhibiting the cyclooxygenase (COX) activity of COX-1 and COX-2 enzymes (Figure 3).[47] Nonselective NSAIDs block the activity of both isoforms. COX-1 mediates prostaglandins that maintain the integrity of the GI, renal, and vascular mucosa and protect surface epithelial cells. COX-2 induces pro-inflammatory prostaglandins that cause the stiffness, swelling, and pain that accompany an illness or injury. Thus, COX-1 inhibition leads to adverse GI and antiplatelet effects; whereas, the inhibition of COX-2 may account for NSAIDs interrupting the inflammatory process.

In patients who are at risk for GI side effects, the clinician might consider management with acetaminophen alone or in combination with a weak opioid or muscle relaxant.[48]

Figure 3

NSAIDs: MECHANISM OF ACTION—THE ROLE OF COX ISOFORMS 1 AND 2 IN NORMAL AND INFLAMED TISSUE[47]



NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase.
Reprinted with permission from Stovitz SD, Johnson RJ. *Phys Sportsmed.* 2003;31:35-40.

Summary

Despite indications that pain is often undertreated, it accounts for a substantial portion of healthcare resources. Uncontrolled pain often results in lost productivity and a poor quality of life. Pain comprises several etiologic factors, all of which can be affected by a number of biomedical, sociocultural, and psychological factors. An effective treatment plan for the management of mild-to-moderate pain consists of both pharmacologic and nonpharmacologic approaches. An array of treatment options and agents is available to manage pain. By weighing the risks and benefits of each agent in relation to the patient's history, clinicians are well positioned to assist their patients in the selection of an appropriate agent that will provide pain relief. Finally, the importance of patient counseling cannot be overlooked. Patients need to be reminded that all medications can be associated with side effects. Patients also need to be reminded that they should read product inserts carefully, not exceed the dosing recommendations, and call their healthcare provider with any questions.

REFERENCES

1. International Association for the Study of Pain. IASP pain terminology. Available at: http://www.iasp-pain.org/terms-p.html#pain. Accessed June 23, 2005.
2. Merskey H, Bogduk N, eds. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definitions of Pain Terms*. 2nd ed. Seattle, Wash: International Association for the Study of Pain (IASP) Press; 1994.
3. Dart RC, Clegg DO. State-of-the-art management of mild-to-moderate pain from adolescence through old age: proceedings highlights. *Clinical Courier®* Vol 22, No. 4. Califon, NJ: SynerMed® Communications; 2004:1-8.
4. Barrett AC, Smith ES, Picker MJ. Sex-related differences in mechanical nociception and antinociception produced by μ- and κ-opioid receptor agonists in rats. *Eur J Pharmacol*. 2002;452:163-173.
5. Riley JL III, Robinson ME, Wise EA, Myers CD, Fillingim RB. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. *Pain*. 1998;74:181-187.
6. Chesterton LS, Barlas P, Foster NE, Baxter GD, Wright CC. Gender differences in pressure pain threshold in healthy humans. *Pain*. 2003;101:259-266.
7. Derbyshire SW, Nichols TE, Firestone L, Townsend DW, Jones AK. Gender differences in patterns of cerebral activation during equal experience of painful laser stimulation. *J Pain*. 2002;3:401-411.
8. Roe CM, McNamara AM, Motheral BR. Gender- and age-related prescription drug use patterns. *Ann Pharmacother*. 2002;36:30-39.
9. Gear RW, Miaskowski C, Gordon NC, Paul SM, Heller PH, Levine JD. Kappa-opioids produce significantly greater analgesia in women than in men. *Nat Med*. 1996;2:1248-1250.
10. Walker JS, Carmody JJ. Experimental pain in healthy human subjects: gender differences in nociception and in response to ibuprofen. *Anesth Analg*. 1998;86:1257-1262.
11. Averbuch M, Katzper M. A search for sex differences in response to analgesia. *Arch Intern Med*. 2000;160:3424-3428.
12. Sheffield D, Biles PL, Orom H, Maixner W, Sheps DS. Race and sex differences in cutaneous pain perception. *Psychosom Med*. 2000;62:517-523.
13. Green CR, Anderson KO, Baker TA, et al. The unequal burden of pain: confronting racial and ethnic disparities in pain. *Pain Med*. 2003;4:277-294.
14. Todd KH, Deaton C, D'Adamo AP, Goe L. Ethnicity and analgesic practice. *Ann Emerg Med*. 2000;35:11-16.
15. Bernabei R, Gambassi G, Lapane K, et al, for the SAGE Study Group. Management of pain in elderly patients with cancer. *JAMA*. 1998;279:1877-1882.
16. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med*. 1994;330:592-596.
17. King CD, Devine DP, Vierck CJ, Rodgers J, Yezierski RP. Differential effects of stress on escape and reflex responses to nociceptive thermal stimuli in the rat. *Brain Res*. 2003;987:214-222.
18. Rhudy JL, Meagher MW. Fear and anxiety: divergent effects on human pain thresholds. *Pain*. 2000;84:65-75.
19. McBeth J, Macfarlane GJ, Hunt IM, Silman AJ. Risk factors for persistent chronic widespread pain: a community-based study. *Rheumatology (Oxford)*. 2001;40:95-101.
20. Gil KM, Ginsberg B, Muir M, Sykes D, Williams DA. Patient-controlled analgesia in postoperative pain: the relation of psychological factors to pain and analgesic use. *Clin J Pain*. 1990;6:137-142.
21. Yelin E, Callahan LF, for the National Arthritis Data Work Group. The economic cost and social and psychological impact of musculoskeletal conditions. *Arthritis Rheum*. 1995;38:1351-1362.
22. Yelin E, Herrndorf A, Trupin L, Sonneborn D. A national study of medical care expenditures for musculoskeletal conditions: the impact of health insurance and managed care. *Arthritis Rheum.* 2001;44:1160-1169.
23. Stewart WF, Ricci JA, Chee E, Morganstein D, Lipton R. Lost productive time and cost due to common pain conditions in the US workforce. *JAMA*. 2003;290:2443-2454.
24. Dawood MY. Dysmenorrhea. *Clin Obstet Gynecol*. 1990;33:168-178.
25. Bloom BS. Direct medical costs of disease and gastrointestinal side effects during treatment for arthritis. *Am J Med*. 1988;84(suppl 2A):20-24.
26. Bertakis KD, Callahan EJ, Helms LJ, Azari R, Robbins JA. The effect of patient health status on physician practice style. *Fam Med*. 1993;25:530-535.
27. Callahan EJ, Bertakis KD, Azari R, Robbins J, Helms LJ, Miller J. The influence of depression on physician-patient interaction in primary care. *Fam Med.* 1996;28:346-351.
28. Callahan EJ, Bertakis KD, Azari R, Robbins JA, Helms LJ, Chang DW. The influence of patient age on primary care resident physician-patient interaction. *J Am Geriatr Soc.* 2000;48:30-35.
29. Bertakis KD, Azari R, Callahan EJ. Patient pain: its influence on primary care physician-patient interaction. *Fam Med.* 2003;35:119-123.
30. Bandura A. Self-efficacy. In: Ramachaudran VS, ed. *Encyclopedia of Human Behavior.* Vol 4. New York, NY: Academic Press; 1994:71-81.
31. Lorig K, Lubeck D, Kraines RG, Seleznick M, Holman HR. Outcomes of self-help education for patients with arthritis. *Arthritis Rheum*. 1985;28:680-685.
32. NIH Technology Assessment Panel on Integration of Behavioral and Relaxation Approaches into the Treatment of Chronic Pain and Insomnia. Integration of behavioral and relaxation approaches into the treatment of chronic pain and insomnia. *JAMA.* 1996;276:313-318.
33. Manyande A, Berg S, Gettins D, et al. Preoperative rehearsal of active coping imagery influences subjective and hormonal responses to abdominal surgery. *Psychosom Med*. 1995;57:177-182.
34. Good M, Anderson GC, Stanton-Hicks M, Grass JA, Makii M. Relaxation and music reduce pain after gynecologic surgery. *Pain Manag Nurs.* 2002;3:61-70.
35. Houle M, McGrath PA, Moran G, Garrett OJ. The efficacy of hypnosis- and relaxation-induced analgesia on two dimensions of pain for cold pressor and electrical tooth pulp stimulation. *Pain*. 1988;33:241-251.
36. Guzman J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary bio-psycho-social rehabilitation for chronic low back pain. *Cochrane Database Syst Rev*. 2002:CD000963.
37. Nielson WR, Weir R. Biopsychosocial approaches to the treatment of chronic pain. *Clin J Pain*. 2001;17(4 suppl):S114-S127.
38. Bardiau FM, Taviaux NF, Albert A, Boogaerts JG, Stadler M. An intervention study to enhance postoperative pain management. *Anesth Analg*. 2003;96:179-185.
39. *Physicians' Desk Reference®* 58th ed. Montvale, NJ: Medical Economics Company, Inc; 2004:1889-1890.
40. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *JAMA*. 2002;287:337-344.
41. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum*. 2000;43:1905-1915.
42. Altman RD, Schweinle JE, Zinsenheim JR, Temple AR. Three-month efficacy and safety of acetaminophen for osteoarthritis pain of the hip or knee. Presented at: 9th World Congress of the Osteoarthritis Research Society International (OARSI); December 2-5, 2004; Chicago, Ill.
43. Power I, Barratt S. Analgesic agents for the postoperative period: nonopioids. *Surg Clin North Am.* 1999;79:275-295.
44. Jones A. Over-the-counter analgesics: a toxicology perspective. *Am J Ther.* 2002;9:245-257.
45. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol.* 1999;26(suppl 56):18-24.
46. Larkai EN, Smith JL, Lidsky MD, Sessoms SL, Graham DY. Dyspepsia in NSAID users: the size of the problem. *J Clin Gastroenterol*. 1989;11:158-162.
47. Stovitz SD, Johnson RJ. NSAIDs and musculoskeletal treatment: what is the clinical evidence? *Phys Sportsmed.* 2003;31:35-40.
48. Della-Giustina D, Kilcline BA, Denny M. Back pain: cost-effective strategies for distinguishing between benign and life-threatening causes. *Emerg Med Pract.* 2000;2:1-24.

OSTEOARTHRITIS

Daniel O. Clegg, MD
Professor of Medicine
Division of Rheumatology
University of Utah School of Medicine
Salt Lake City, Utah

Richard C. Dart, MD, PhD
Director, Rocky Mountain Poison and Drug Center, Denver Health
Professor of Surgery (Emergency Medicine)
University of Colorado Health Sciences Center
Denver, Colorado

Arnold P. Advincula, MD
Clinical Assistant Professor
Director, Minimally Invasive Surgery and Chronic Pelvic Pain Program
Department of Obstetrics and Gynecology
University of Michigan Medical Center
Ann Arbor, Michigan

Kathleen B. Digre, MD
Professor of Ophthalmology and Neurology
John A. Moran Eye Center
University of Utah School of Medicine
Salt Lake City, Utah

Steven Stovitz, MD, CAQSM
Assistant Professor
Department of Family Practice and Community Health
University of Minnesota
Minneapolis, Minnesota

Cheryl Wright, MD
Department of Rheumatology
Sharp Rees-Stealy Medical Center
San Diego, California

OSTEOARTHRITIS

The deficiencies of pain management are perhaps nowhere more apparent than in the treatment of osteoarthritis (OA). According to the American College of Rheumatology (ACR), OA is the most common form of arthritis in the United States,[1,2] and joint pain is the reason patients most often seek treatment.[3] OA and other forms of arthritis are a significant cause of morbidity and disability and are responsible for direct and indirect costs of approximately $65 billion each year.[4] Radiographic evidence of OA in at least 1 joint is apparent in the majority of persons by 65 years of age and in nearly 70% of the population older than 65 years of age.[2,5] The elderly population in the United States continues to increase, making OA a significant medical and economic concern. It has been estimated that the prevalence of OA will more than double by 2020; by 2030, approximately 70 million people, or 20% of the population, will be older than 65 years of age and at greater risk for developing the disease.[1,2]

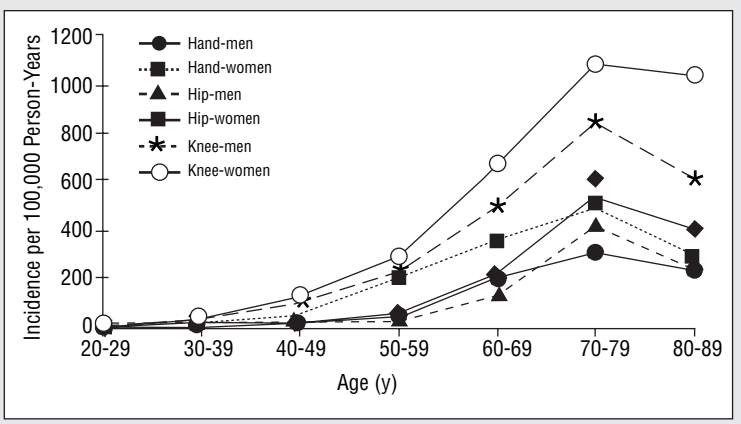
Although there is no known cure for OA, there are several aspects of OA management that have improved in recent years, including earlier recognition of the disease and its risk factors, as well as an increased understanding of adverse events associated with some of the available treatments. Multiple advances in the understanding of this disease mean OA can no longer be dismissed as a simple consequence of aging and cartilage degeneration, but rather it is a condition whose symptoms—primarily pain—can be managed effectively with a combination of pharmacologic and nonpharmacologic measures. By increasing awareness of the risk factors for the disease and understanding the benefits and limitations of each of the treatment options, the clinician can help patients recognize developing symptoms of the disease sooner and provide prompt and effective treatment.

OA Risk Factors

OA affects millions of people in the United States. Goals of OA therapy are to relieve pain, minimize disability, and delay or prevent disease progression. Risk factors for OA include variables such as female gender and increasing age, which increase susceptibility. Additionally, local biomechanical variables such as joint injury and obesity affect site and severity of OA.[6] The incidence of OA increases with age, and gender-specific differences are evident. Before 50 years of age, the prevalence of OA in most joints is higher in men than in women. After age 50, women are more often affected with hand, foot, and knee OA. In a community-based survey, the incidence and prevalence of OA increased 2- to 10-fold from 30 to 65 years of age and increased further thereafter (Figure 1).[7]

Figure 1

INCIDENCE OF OA[7]



OA, osteoarthritis.

Diagnosis

Although it is not possible to diagnose OA with a single test, clinicians use a combination of the patient's clinical history, physical examination, and x-rays to diagnose the disease. The clinical features of OA are summarized in Table 1.[3] Patients typically present with mild-to-moderate pain and/or stiffness in or around the affected joint, which is often associated with some degree of functional limitation and is usually insidious in onset. Pain typically worsens with use of the affected joint, but is alleviated at rest, with nocturnal pain or pain at rest being indicative of severe disease.[3]

Table 1

CLINICAL FEATURES OF OA[3]

Symptoms	Signs
Joint pain	Bony enlargement at affected joints
Morning stiffness <30 minutes	Limitation of range of motion
Gel phenomenon	Crepitus on motion
Joint instability/buckling	Pain with motion
Loss of function	Tenderness with pressure
	Joint effusion
	Malalignment and/or joint deformity

OA, osteoarthritis.
Adapted with permission from Creamer P, Hochberg MC. *Lancet.* 1997;350:503-509.

Table 2

CLASSIFICATION CRITERIA FOR OA[9-11]

Location of Pain	Features
Hand	3 or 4 of the following*: • Hard tissue enlargement of 2 or more of 10 selected joints • Hard tissue enlargement of 2 or more DIP joints • Fewer than 3 swollen MCP joints • Deformity of at least 1 of 10 selected joints
Hip	At least 2 of the following 3†: • ESR <20 mm/hour • Radiographic femoral or acetabular osteophytes • Radiographic joint-space narrowing (superior, axial, and/or medial)
Knee	Osteophytes on radiographs and at least 1 of the following: • Patient age >50 years • Morning stiffness <30 minutes in duration • Crepitus on motion

OA, osteoarthritis; DIP, distal interphalangeal; MCP, metacarpophalangeal; ESR, erythrocyte sedimentation rate.

*The 10 selected joints are the second and third DIP joints, the second and third proximal interphalangeal, and the first carpometacarpal joints of both hands. This classification method yields a sensitivity of 94% and a specificity of 87%.

†This classification method yields a sensitivity of 89% and a specificity of 91%.

A clinical diagnosis usually can be confirmed by x-ray. The cardinal radiographic features are asymmetrical joint-space narrowing, marginal osteophytes, and subchondral bone sclerosis and cyst formation, and, in the presence of severe disease, there is deformity of bone ends.[3] Although evidence of mild inflammation may be present, it is not a hallmark of OA.[3] In most patients with OA, routine blood tests, including complete blood count (CBC) and chemistry panel, are normal. However, the American Academy of Orthopaedic Surgeons Clinical Practice Guidelines recommend that patients who are planning to use nonsteroidal anti-inflammatory drugs (NSAIDs) in the long term should have a CBC, renal and liver function tests, and a stool guaiac every 6 months.[8]

OA affects synovial joints, which leads to a progressive loss of articular cartilage and reactive changes at the joint margins and in the subchondral bone. The most common sites of OA are the hands, followed by the feet, knees, and hips.[3] Articular damage tends to concentrate in the primary weight-bearing joints, typically the hips and knees, but other sites can be affected, including the spine, the distal interphalangeal joints (Heberden's nodes), and the proximal interphalangeal joints (Bouchard's nodes). In order to assist the clinician with the diagnosis of different subsets of OA, the ACR has developed classification criteria for OA of the hand, hip, and knee (Table 2).[9-11]

OA Management

The management of OA focuses on symptom—primarily pain—control and risk modification.[3] Treatment guidelines for hip and knee OA have been published by the ACR and the European League Against Rheumatism (EULAR), both of which were developed from a combination of expert opinion and an evidence-based analysis of the available literature.[12,13] Although each of these guidelines differs in terms of the methodologies used and recommendations made, areas of consensus have been achieved for several pharmacologic, nonpharmacologic, and surgical interventions (Table 3).[12-14]

Both sets of guidelines agree that the optimal management of OA is multimodal and necessitates the combination of pharmacologic and nonpharmacologic treatment modalities based on the individual needs of the patient. Individualizing treatment includes the consideration of any comorbid conditions, such as peptic ulcer disease, cardiac disease, hypertension, or renal disease, when selecting the most appropriate pharmacologic treatment. Furthermore, these organizations concur that

nonpharmacologic options such as exercise, patient education, and weight loss are the most effective nonpharmacologic approaches and serve as the foundation of an individualized management plan.

Overall, evidence shows that quadriceps strengthening can increase knee extensor strength in both males and females.[15,16] Manual physical therapy (PT) also increases strength as demonstrated on Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores.[17] Results of randomized, controlled trials suggest that PT diminishes OA pain by 8% to 56%.[16-18] In addition to exercise, weight loss has been shown to provide improvements in function and pain and in performance measures of mobility in older overweight and obese adults with knee OA.[19]

Analgesia

The cornerstone of multimodal therapy is analgesia. Both the ACR and the EULAR guidelines advocate the use of acetaminophen as a first-line therapy for mild-to-moderate OA.[12,13] This recommendation has been supported by the results of a recent randomized, double-blind, parallel-group trial assessing 483 patients with moderate-to-severe OA of the hip or knee.[20] Results showed that subjects taking 3900-mg acetaminophen extended-release caplets daily (two 650-mg caplets tid) had significantly less pain and more improved physical function than did placebo-treated patients. Acetaminophen was superior to placebo for WOMAC pain score and WOMAC physical function score (Figure 2),[20] with similar results for both knee and hip OA. Furthermore, there were no significant differences between treatment groups regarding the use of rescue medication and WOMAC stiffness subscale scores.

Other available agents are nonselective and cyclooxygenase-2–selective NSAIDs, centrally acting analgesic agents, and adjuvants such as tricyclic antidepressants and muscle relaxants. If the maximum recommended dosage of acetaminophen (4000 mg/d) does not provide adequate analgesia, analgesic doses of NSAIDs should be tried.[12]

In a recent meta-analysis that assessed the analgesic efficacy of selective and nonselective NSAIDs in patients with OA of the knee, investigators found that NSAIDs can reduce short-term pain in knee OA slightly better than can placebo. However, one of the studies that provided long-term data for pain relief demonstrated no significant effect of NSAIDs compared with placebo at 1 to 4 years.[21]

Although further controlled, comparative trials are warranted, acetaminophen and NSAIDs appear to be equally efficacious in treating pain associated with mild-to-moderate OA.[22,23] However, acetaminophen can provide effective pain relief for patients seeking an alternative to prescription analgesics[20] or for whom NSAID therapy is not recommended. As always, benefits of therapy must be carefully compared with the inherent risks associated with each agent.

For other modalities, evidence is less consistent. Strong efficacy evidence in favor of sodium hyaluronate injections is lacking. Two of 3 large randomized, controlled trials failed to demonstrate

Table 3

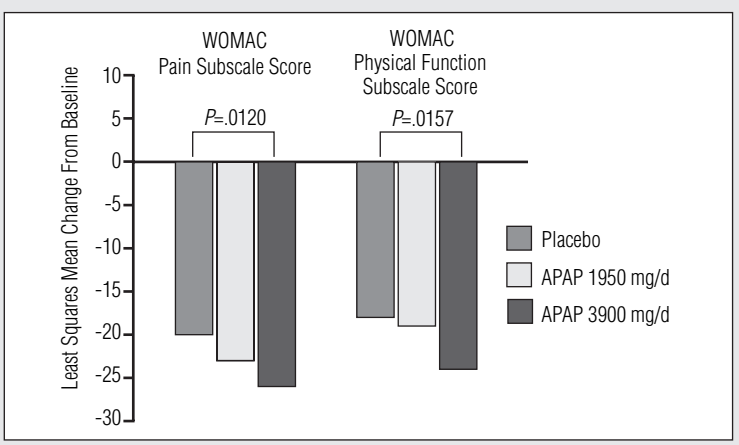
ACR AND EULAR RECOMMENDATIONS ON THE MANAGEMENT OF OA[12-14]

Nonpharmacologic Therapy	Pharmacotherapy	Surgery
• Patient education	• Acetaminophen	• Arthroplasty
• Personalized social support	• NSAID	
• Weight loss	• IA corticosteroid	
• Aerobic exercise	• Topical NSAID	
• Muscle strengthening	• IA hyaluronate	
• Range-of-motion exercises		
• Walking aids		
• Insoles		

ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; OA, osteoarthritis; NSAID, nonsteroidal anti-inflammatory drug; IA, intra-articular.

Figure 2

ACETAMINOPHEN EFFICACY: MEAN CHANGE AT WEEK 12 FOR PRIMARY ENDPOINTS[20]



WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; APAP, acetaminophen.

Reprinted with permission from Altman RD et al. Presented at: 9th World Congress of the Osteoarthritis Research Society International (OARSI); December 2-5, 2004; Chicago, Ill.

clear-cut benefits compared to placebo.[24-26] For arthroscopy, a 2-year study showed no differences among debridement, lavage, or placebo.[27] Glucosamine and chondroitin are also widely utilized for treating OA. Efficacy data are mixed and results of carefully designed studies are pending. There are data suggesting that glucosamine may delay disease progression in knee joints.[28,29]

Summary

Current evidence on the management of OA supports the utility of a multimodal approach combining nonpharmacologic therapy, such as weight loss, exercise, patient education, and behavioral programs, with systemic pharmacologic therapy for the treatment of pain.

References

1. Lawrence RC, Helmick CG, Arnett FC, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum.* 1998;41:778-799.
2. National Institute of Arthritis and Musculoskeletal and Skin Diseases. Handout on health: osteoarthritis. National Institutes of Health. Available at: http://www.niams.nih.gov/hi/topics/arthritis/oahandout.htm. Accessed April 20, 2004.
3. Creamer P, Hochberg MC. Osteoarthritis. *Lancet.* 1997;350:503-509.
4. National Arthritis Action Plan. A public health strategy. Available at: http://www.cdc.gov/nccdphp/pdf/naap.pdf. Accessed June 20, 2004.
5. Lane NE, Thompson JM. Management of osteoarthritis in the primary-care setting: an evidence-based approach to treatment. *Am J Med.* 1997;103:25S-30S.
6. Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med.* 2000;133:635-646.
7. Oliveria SA, Felson DT, Reed JI, Cirillo PA, Walker AM. Incidence of symptomatic hand, hip, and knee osteoarthritis among patients in a health maintenance organization. *Arthritis Rheum.* 1995;38:1134-1141.
8. American Academy of Orthopaedic Surgeons. AAOS clinical guidelines on osteoarthritis of the knee. Available at: http://www.guideline.gov/summary/summary.aspx?ss=15&doc_id=3856&nbr=3069&string=#s23. Accessed March 29, 2005.
9. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum.* 1991;34:505-514.
10. Altman R, Alarcon G, Appelrouth D, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. *Arthritis Rheum.* 1990;33:1601-1610.
11. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. *Arthritis Rheum.* 1986;29:1039-1049.
12. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. *Arthritis Rheum.* 2000;43:1905-1915.
13. Pendleton A, Arden N, Dougados M, et al. EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). *Ann Rheum Dis.* 2000;59:936-944.
14. Roddy E, Doherty M. Guidelines for management of osteoarthritis published by the American College of Rheumatology and the European League Against Rheumatism: why are they so different? *Rheum Dis Clin North Am.* 2003;29:717-731.
15. Slemenda C, Brandt KD, Heilman DK, et al. Quadriceps weakness and osteoarthritis of the knee. *Ann Intern Med.* 1997;127:97-104.
16. O'Reilly SC, Muir KR, Doherty M. Effectiveness of home exercise on pain and disability from osteoarthritis of the knee: a randomised controlled trial. *Ann Rheum Dis.* 1999;58:15-19.
17. Deyle GD, Henderson NE, Matekel RL, Ryder MG, Garber MB, Allison SC. Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee: a randomized, controlled trial. *Ann Intern Med.* 2000;132:173-181.
18. Ettinger WH Jr, Burns R, Messier SP, et al. A randomized trial comparing aerobic exercise and resistance exercise with a health education program in older adults with knee osteoarthritis: the Fitness Arthritis and Seniors Trial (FAST). *JAMA.* 1997;277:25-31.
19. Messier SP, Loeser RF, Miller GD, et al. Exercise and dietary weight loss in overweight and obese older adults with knee osteoarthritis: the Arthritis, Diet, and Activity Promotion Trial. *Arthritis Rheum.* 2004;50:1501-1510.
20. Altman RD, Schweinle JE, Zinsenheim JR, Temple AR. Three-month efficacy and safety of acetaminophen for osteoarthritis pain of the hip or knee. Presented at: 9th World Congress of the Osteoarthritis Research Society International (OARSI); December 2-5, 2004; Chicago, Ill.
21. Bjordal JM, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. *BMJ*, doi:10.1136/bmj.38273.626655.63 (published 23 November 2004).
22. Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI. Comparison of an antiinflammatory dose of ibuprofen, an analgesic dose of ibuprofen, and acetaminophen in the treatment of patients with osteoarthritis of the knee. *N Engl J Med.* 1991;325:87-91.
23. Williams HJ, Ward JR, Egger MJ, et al. Comparison of naproxen and acetaminophen in a two-year study of treatment of osteoarthritis of the knee. *Arthritis Rheum.* 1993;36:1196-1206.
24. Felson DT, Anderson JJ. Hyaluronate sodium injections for osteoarthritis: hope, hype, and hard truths. *Arch Intern Med.* 2002;162:245-247.
25. Puhl W, Bernau A, Greiling H, et al. Intra-articular sodium hyaluronate in osteoarthritis of the knee: a multicentre double-blind study. *Osteoarthritis Cartilage.* 1993;1:233-241.
26. Altman RD, Moskowitz R, and the Hyalgan® Study Group. Intraarticular sodium hyaluronate (Hyalgan®) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. *J Rheumatol.* 1998;25:2203-2212.
27. Moseley JB, O'Malley K, Petersen NJ, et al. A controlled trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med.* 2002;347:81-88.
28. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. *Arch Intern Med.* 2002;162:2113-2123.
29. Reginster JY, Deroisy R, Rovati LC, et al. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet.* 2001;357:251-256.

COMMON PAIN CONDITIONS

Daniel O. Clegg, MD
Professor of Medicine
Division of Rheumatology
University of Utah School of Medicine
Salt Lake City, Utah

Richard C. Dart, MD, PhD
Director, Rocky Mountain Poison and
Drug Center, Denver Health
Professor of Surgery
(Emergency Medicine)
University of Colorado
Health Sciences Center
Denver, Colorado

Arnold P. Advincula, MD
Clinical Assistant Professor
Director, Minimally Invasive Surgery
and Chronic Pelvic Pain Program
Department of Obstetrics and Gynecology
University of Michigan Medical Center
Ann Arbor, Michigan

Kathleen B. Digre, MD
Professor of Ophthalmology
and Neurology
John A. Moran Eye Center
University of Utah School of Medicine
Salt Lake City, Utah

Steven Stovitz, MD, CAQSM
Assistant Professor
Department of Family Practice and
Community Health
University of Minnesota
Minneapolis, Minnesota

Cheryl Wright, MD
Department of Rheumatology
Sharp Rees-Stealy Medical Center
San Diego, California

The Role of Inflammation in Musculoskeletal Healing

According to the National Center for Health Statistics, more physician visits were made in 2000 for musculoskeletal symptoms than for any other reason.[1] Injuries to tendons, ligaments, muscles, and bones can cause significant pain, which is often accompanied by inflammation. Although this inflammation may be associated with pain, it is also fundamental to the healing of musculoskeletal injuries. Historically, the anti-inflammatory effect of nonsteroidal anti-inflammatory drugs (NSAIDs) has been the rationale for using these analgesics in the treatment of musculoskeletal injuries; however, the clinician must evaluate the role inflammation plays in wound healing when prescribing an analgesic for pain.

Musculoskeletal Injuries and Wound Healing

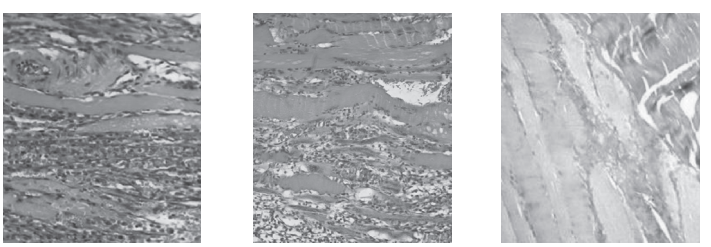
Wound healing occurs in 3 phases: inflammation, proliferation, and maturation, each of which is essential to the subsequent phase[2] (Figure 1a-c). Inflammation starts immediately with an influx of inflammatory cells, which recruit additional macrophages to the injury site. Macrophages invade the damaged muscle fiber and destroy cellular debris and damaged myofibrillar material.[3] In the proliferative phase, macrophages continue to remove debris and produce growth factors, which recruit fibroblasts and cytokines that may regulate the proliferation or differentiation of myoblasts, the cells that create new muscle tissue.[3] Finally, in the maturation phase, fibroblasts lay down collagen and tissue remodeling takes place.

The course of this process is variable—it can take days to months depending on the extent of the injury, the patient's systemic health, and the blood supply to the tissue involved. It is necessary for the clinician to recognize that inflammation and repair are part of a single process and that the choice of analgesic during this crucial inflammatory phase may theoretically have a negative impact on the healing process.

Rest, ice, compression, and elevation are often recommended for patients with musculoskeletal injuries; however, strong data supporting these interventions are lacking. Whereas acetaminophen may be expected to reduce pain without disrupting the vital inflammation process in many of these injuries, to date no placebo-controlled studies have been conducted to evaluate its use in these types of injuries. The clinical utility of nonspecific NSAIDs is debatable, as conflicting results have been reported in clinical trials.[4,5] There is some evidence from animal studies that the suppression of inflammation caused by cyclooxygenase (COX)-2 inhibition may actually be detrimental to mechanical healing, especially in the early healing phase.[4] However, animal data cannot necessarily be extrapolated to humans. The initial inflammatory phase is partly mediated by the same prostaglandins that are blocked by NSAIDs. If the initial healing phase is blocked, it may inhibit the subsequent proliferative and maturation phases, which could delay the healing of musculoskeletal injuries.[5]

Figure 1a-c

RESPONSE TO INJURY



a) Inflammatory phase b) Proliferative phase c) Maturation phase

Courtesy of D.O. Clegg, MD.

Although recommended doses of over-the-counter (OTC) nonspecific NSAIDs are generally too low to cause significant suppression of inflammation, many are taken at higher doses. Until the relationship between NSAID use and healing is better understood, it may be best to recommend that patients utilize the lowest dose of an NSAID that provides effective analgesia.

Tendon Injuries

The traditional view of tendon injury proposed that swelling and pain resulted from repetitive mechanical load with a subsequent inflammatory response, hence the suffix "itis," and therapy focused on reducing pain and inflammation with rest, ice, and anti-inflammatory medications. In tendinitis, which more accurately should be termed tendinopathy or tendinosis, there is actually no clinically apparent inflammation, so an anti-inflammatory agent is unlikely to be beneficial. In support of this, Almekinders and Temple conducted a literature review of 2326 articles on the etiology, diagnosis, and treatment of "tendinitis"; they concluded that actual inflammation of tendon tissue consistent with tendinitis has not been demonstrated clearly in pathoanatomic studies.[6]

Chronic tendon injuries such as tennis elbow are often assigned the misnomer tendinitis. However, biopsy studies have demonstrated that these injuries are due to microtrauma of the tendon, with pain arising from degeneration rather than inflammation.[7,8] For tendon degeneration without signs of inflammatory response, the more appropriate term is tendinosis, and all pathologies that arise in and around the tendons are called tendinopathy. The differences between these terms are not merely semantic; there are clinical implications, as well. For instance, the treatment of tendinosis needs to target the breakdown of collagen rather than inflammation.[9]

Less is known about acute tendon injuries. One theory suggests that tissue damage in overuse tendinopathy may actually precede acute injury and overt symptoms.[10] In sports medicine, a typical scenario is a period of excessive training that precedes the development of symptoms. An athlete might complain of elbow pain after lifting a heavy suitcase, but there is really no way to determine whether this is an acute injury or simply the result of preexisting tendon damage.

Because NSAIDs have both analgesic and anti-inflammatory effects, NSAID use has been widely emphasized in the treatment of sports-related injuries. Theoretically, however, their anti-inflammatory effects would appear to have little therapeutic benefit in tendinosis.[7] In the review by Almekinders and Temple, investigators found only 9 prospective, placebo-controlled studies assessing NSAIDs and chronic tendon injuries.[6] Five of these studies showed improved pain scores in the NSAID group, with a maximum follow-up of only 1 to 4 weeks. According to the authors, there is insufficient evidence to determine whether NSAIDs actually change the natural course of healing or whether improvement is due to the analgesic action of these agents.

There are also clinical implications for physiotherapy in the healing process. For example, rest has historically been recommended with the hope that it would quell inflammation. However, rest could increase the risk of tendon degeneration. Conversely, eccentric muscle training would likely increase inflammation and decrease the risk of degeneration. In fact, when compared to conventional treatment (ie, rest, NSAIDs, physical therapy) and concentric training, eccentric training has demonstrated superior results in chronic Achilles tendinosis.[11,12] Analgesics may help the rehabilitation process by relieving pain and allowing the patient to rehabilitate appropriately.

Muscle Injuries

The most frequent types of sports-related muscle injuries are strains, contusions, and delayed-onset muscle soreness (DOMS).[13] Strain injuries are the result of excessive tension on the muscle, which results in a tear, followed by inflammation, clearing of debris, and, finally, regeneration of the muscle. Animal studies have demonstrated that NSAIDs may result in some small negative effects in the healing phase,[13] but only 1 study has been conducted in humans.[14]

The clinical evidence of NSAID efficacy in contusions is also lacking. Although animal studies have shown a slight delay in early inflammation and a later decrease in tensile properties in the NSAID-treated groups, there have been no recent studies in humans on the relation of NSAID use to the recovery of muscle contusion injuries.[13,15]

In general, DOMS begins 24 to 48 hours after intense eccentric muscle use. Consensus is that inflammation is not an essential feature of DOMS; therefore, NSAID use is not likely to be of great benefit. Human studies bear this out—as a whole, they are equivocal as to whether or not NSAIDs help or hinder the resolution of DOMS.[13]

Bone Remodeling—A Natural Inflammatory Process

Healthy bone undergoes constant remodeling as part of the normal skeletal maintenance process, and fractured bone undergoes the same, albeit a more intense, inflammatory process in response to healing. Prostaglandins, especially prostaglandin E_2, have multiple effects on the resorption and stimulation of bone growth. NSAIDs inhibit osteoclastic and osteoblastic activity, which could increase the risk of fracture or inhibit fracture healing.

In a retrospective cohort study of 214,577 regular NSAID users, 286,850 incidental NSAID users, and 214,577 control patients, investigators sought to describe and quantify the fracture risks of patients exposed to NSAIDs.[16] Results showed that NSAID use was associated with a relative risk of nonvertebral fractures of 1.47 as compared to non-NSAID use. In addition, NSAID use has been shown to inhibit fracture healing. A retrospective analysis of patients with diaphysis fracture of the femur showed a marked association between nonunion of the fracture and the use of NSAIDs after injury (P=.000001), and delayed healing was noted in patients who took NSAIDs and whose fractures had united.[17]

Acute and Chronic Low Back Pain

Most adults have experienced back pain at some point in their lives. National statistics reflect an annual prevalence in the US population of 15% to 20%.[18] Among working-age people, 50% admit to back symptoms each year.[18] Low back problems are the most common cause of disability for persons under 45 years of age, and the economic consequences of back pain are substantial. Approximately 175 million workdays per year are lost, amounting to $20 billion in lost productivity.[18] The medical costs to society are also high, with almost $5 billion per year spent on surgery alone for chronic back pain.[19]

Low back pain is typically classified according to its duration (ie, acute or chronic). Acute pain (less than 3 months in duration) is usually mechanical and self-limiting. Chronic pain, however, is more difficult to treat—those slowest to recover with reduced activity at 12 weeks face the prospect of being disabled for longer than 6 months with a return-to-work rate close to zero after 2 years of absence.[20]

Differential diagnosis of low back pain should distinguish between mechanical, nonmechanical, visceral, or referred pain (Table 1, page 16).[21] Ninety-seven percent of low back problems are mechanical in nature, due to muscle strain, degenerative processes of disks and facets, spinal stenosis, or herniated disk.[21] Nonmechanical causes of back pain are infection, cancer, and inflammatory arthritis. Visceral low back pain can be caused by diseases of the renal, gastrointestinal (GI), and pelvic systems or by aortic aneurysm.[21]

Most patients with low back problems recover quickly without residual functional loss. In fact, 60% to 70% of back problems resolve within 6 weeks and 80% to 90% by week 12.[20] The natural history of herniated disks is also favorable—only about 10% of patients have sufficient pain after 6 weeks to make surgery a consideration. The herniated portion of the disk tends to regress over time, with partial or complete resolution in two thirds of cases after 6 months.[21]

Nonpharmacologic Treatment for Low Back Pain

The Agency for Health Care Policy and Research clinical practice guidelines for low back pain assessed the effectiveness of various physical modalities for the treatment of acute low back pain. They recommended patient education and spinal manipulation within the first month of symptoms.[22] However, there is insufficient evidence to support the use of traction, thermotherapy, ultrasound, cutaneous laser treatment, transcutaneous electrical nerve stimulation (TENS), biofeedback techniques, and back school. Prolonged bedrest is also not recommended, as bedrest for more than 4 days may lead to debilitation.[22,23] Exercise therapy, in addition to medical management and resumption of normal activity, may be more effective in reducing low back pain recurrences than medical management and normal activity alone.[24]

For chronic pain, therapeutic exercise has demonstrated efficacy, but there is no evidence to support the use of traction, ultrasound, TENS, or electromyographic biofeedback.[23] There are insufficient data to support the use of thermotherapy, massage, or electrical stimulation in the treatment of chronic pain.[23]

Pharmacologic Treatment for Acute and Chronic Back Pain

A multidisciplinary approach to the treatment of low back problems combines pharmacologic and nonpharmacologic treatments aimed at early intervention and symptom control in order to reduce pain and improve function and quality of life. Pharmacologic options are similar for both acute and chronic back pain: acetaminophen, nonselective and selective NSAIDs, muscle relaxants, acetaminophen combination products, and opioids. In addition, chronic back pain has been treated with tricyclic antidepressants.[25,26]

In a meta-analysis, NSAIDs were found to be more effective than placebo for acute back pain.[27] Efficacy studies comparing NSAIDs with acetaminophen revealed conflicting results, suggesting that they are comparable.[27] NSAIDs may not be more effective than other drugs for acute low back pain, and differences among NSAIDs have not been demonstrated. In addition, NSAIDs have not been proven to be more effective than physiotherapy or spinal manipulation.[27]

Prescription options for patients who do not experience adequate pain relief with maximum

Table 1

DIFFERENTIAL DIAGNOSIS OF LOW BACK PAIN*[21]

Mechanical Low Back or Leg Pain (97%)†

Lumbar strain, sprain (70%)§

Degenerative processes of disks and facets, usually age-related (10%)

Herniated disk (4%)

Spinal stenosis (3%)

Osteoporotic compression fracture (4%)

Spondylolisthesis (2%)

Traumatic fracture (<1%)

Congenital disease (<1%)
- Severe kyphosis
- Severe scoliosis
- Transitional vertebrae

Spondylolysis¶

Internal disk disruption or diskogenic low back pain#

Presumed instability**

Nonmechanical Spinal Conditions (About 1%)‡

Neoplasia (0.7%)
- Multiple myeloma
- Metastatic carcinoma
- Lymphoma and leukemia
- Spinal cord tumors
- Retroperitoneal tumors
- Primary vertebral tumors

Infection (0.01%)
- Osteomyelitis
- Septic diskitis
- Paraspinous abscess
- Epidural abscess
- *Shingles*

Inflammatory arthritis (often associated with HLA-B27) (0.3%)
- Ankylosing spondylitis
- Psoriatic spondylitis
- Reiter's syndrome
- Inflammatory bowel disease

Scheuermann's disease (osteochondrosis)

Paget's disease of bone

Visceral Disease (2%)

Disease of pelvic organs
- Prostatitis
- Endometriosis
- Chronic pelvic inflammatory disease

Renal disease
- Nephrolithiasis
- Pyelonephritis
- Perinephric abscess

Aortic aneurysm

Gastrointestinal disease
- Pancreatitis
- Cholecystitis
- Penetrating ulcer

*Figures in parentheses indicate the estimated percentages of patients with these conditions among all adult patients with low back pain in primary care. Diagnoses in italics are often associated with neurogenic leg pain. Percentages may vary substantially according to demographic characteristics or referral patterns in a practice. For example, spinal stenosis and osteoporosis will be more common among geriatric patients, spinal infection among injection-drug users, and so forth.

†The term "mechanical" is used here to designate an anatomic or functional abnormality without an underlying malignant, neoplastic, or inflammatory disease. Approximately 2% of cases of mechanical low back or leg pain are accounted for by spondylolysis, internal disk disruption or diskogenic low back pain, and presumed instability.

‡Scheuermann's disease and Paget's disease of bone probably account for less than 0.01% of nonmechanical spinal conditions.

§"Strain" and "sprain" are nonspecific terms with no pathoanatomic confirmation. "Idiopathic low back pain" may be a preferable term.

¶Spondylolysis is as common among asymptomatic persons as among those with low back pain, so its role in causing low back pain remains ambiguous.

#Internal disk disruption is diagnosed by provocative diskography (injection of contrast material into a degenerated disk, with assessment of pain at the time of injection). However, diskography often causes pain in asymptomatic adults, and the condition of many patients with positive diskograms improves spontaneously. Thus, the clinical importance and appropriate management of this condition remain unclear. "Diskogenic low back pain" is used more or less synonymously with "internal disk disruption."

**Presumed instability is loosely defined as greater than 10 degrees of angulation or 4 mm of vertebral displacement on lateral flexion and extension radiograms. However, the diagnostic criteria, natural history, and surgical indications remain controversial.

recommended doses of a first-line OTC analgesic include therapeutic doses of NSAIDs for those who are not at risk for heart disease, kidney disease, or GI events,[28-30] or the initiation of a prescription COX-2 inhibitor for those who have a low risk for cardiovascular (CV) events, but are at high risk for GI events. Because COX-2 inhibitors are generally associated with reduced risk for GI and hematologic toxicities, they may be preferred over nonspecific NSAIDs in certain at-risk populations.

Muscle relaxants may be recommended for patients experiencing moderate-to-severe low back pain. Cyclobenzaprine, the only muscle relaxant that has been well studied in the treatment of this condition, provides only modest relief of symptoms compared with placebo and is associated with drowsiness.[31] A lower-dose regimen may cause less drowsiness than that observed in earlier studies with the higher-dose regimen.[32] Symptom relief is greatest early; therefore, long-term use is generally not recommended. In the primary care setting, muscle relaxants are used frequently in combination with NSAIDs for acute back pain. In a single longitudinal study of 219 patients, such combinations were associated with improved patient outcomes versus those with NSAIDs alone, muscle relaxants alone, narcotics, and acetaminophen.[33]

For chronic back pain, opioids may provide significantly better results than do NSAIDs. In a small randomized, controlled trial comparing naproxen to either oxycodone or oxycodone plus sustained-release morphine, patients experienced significantly less pain with the opioid treatments than with naproxen. No significant abuse potential was observed, but benefits disappeared when doses were tapered.[34] Antidepressants also have some utility in chronic back pain in patients without depression, but the effect may be modest.[25] Injection therapy for chronic back pain is medically accepted, but definitive evidence of benefit is lacking.[35]

Tramadol is a centrally acting, nonnarcotic, nonscheduled synthetic opioid agonist that is also available in a prescription combination product that combines tramadol 37.5 mg with acetaminophen 325 mg. Tramadol is generally better tolerated than are other opioid analgesics[36] and provides effective analgesia for a number of pain states, including back pain and OA.[36-38]

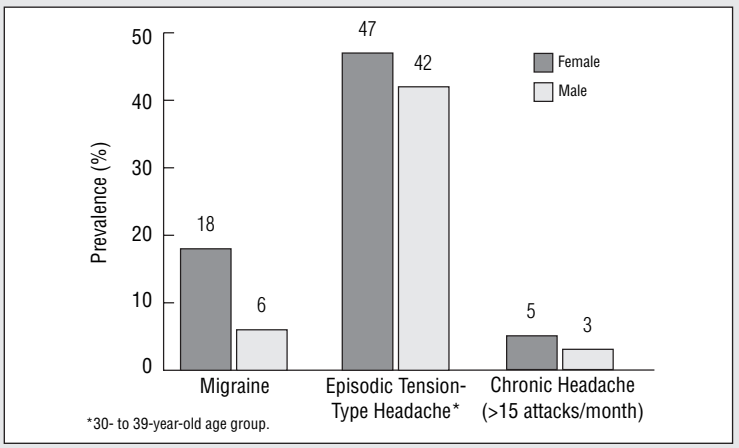
Headache—A Focus on Migraine

Improved understanding of migraine pathogenesis and pain mechanisms has changed headache management strategies substantially. Once thought to be a vascular headache, migraine is now understood to be a neurovascular disorder. Genetic susceptibility, neuronal hyperexcitability, and cortical, trigeminal, and periaqueductal participation are all thought to contribute to the pathogenesis of migraine headaches.[39] Given its substantially greater prevalence in women, migraine may also be influenced by gender differences in developmental and hormonal variables. For instance, menstrual migraine is one well-recognized, migraine subtype.

The Headache Classification Subcommittee of the International Headache Society has defined 3 primary headache disorders: migraine with and without aura, tension-type headache, and cluster headache.[40] By far, the most common headache disorder in the general population is episodic tension-type headache, which affects approximately 40% of the population (Figure 2).[41-44] Both migraine and tension-type headaches are common among women (18%[44] and 47%,[42] respectively). Migraine, which affects 28 million people 12 years of age or older in the United States,[44] is characterized by recurring (>5 attacks), long-lasting (4 to 72 hours) headaches. Diagnosis requires that at least 2 of the following be present: unilateral pain, throbbing pain, moderate-to-severe pain, or pain that worsens with activity. Patients must also report nausea and/or vomiting or photophobia and phonophobia.[40] In contrast, tension headaches are typically mild-to-moderate in intensity, bilateral, have a pressing/tightening quality, and are not aggravated by routine physical activity. Nausea and vomiting are typically absent as is photophobia or phonophobia. (Patients with tension headaches may report photophobia or phonophobia, but not both.[40])

Figure 2

ONE-YEAR PREVALENCE OF COMMON HEADACHE DISORDERS[41-44]



Preventive therapy is recommended for patients with migraine headaches that substantially affect their lives; however, effective therapies are largely underutilized.[45] According to the US Headache Consortium, the goals of preventive therapy for migraine are to: (1) reduce attack frequency, severity, and duration, (2) improve responsiveness to treatment of acute attacks, and (3) improve function and reduce disability.[45] Management involves accurate diagnosis, assessment of disability and comorbidities, patient education and participation, and pharmacologic treatment. Pharmacologic treatments encompass acute and preventive approaches. Some of the most effective medications are pathology directed (eg, triptans in acute treatment, anticonvulsant agents in prevention). Acute management is intended to treat attacks and restore function. Acute therapies are grouped with respect to evidence-based degree of benefit (Table 2, page 18).[46]

While the Headache Consortium did not find acetaminophen to be helpful in the treatment of migraine, a randomized, double-blind, placebo-controlled, population-based study did. In this study, completed after the guidelines were published, Lipton and colleagues found that acetaminophen was highly effective for headaches and migraine and had an excellent safety profile.[47]

Patients who suffer from migraine should be made aware of the role that nonpharmacologic

Table 2

EVIDENCE BASIS FOR ACUTE THERAPIES IN MIGRAINE TREATMENT[46]

Clear Benefit	Moderate Benefit	No/Unknown Benefit
Over-the-counter	Opioids	Benefit not established
• Aspirin	• Acetaminophen, codeine	• Butalbital, aspirin, caffeine
• Aspirin, caffeine	• Meperidine	• Ergotamine with or without caffeine (PO)*
• Acetaminophen, aspirin, caffeine	• Methadone	• Metoclopramide (IM, PR)
Nonspecific	• Butalbital, aspirin, caffeine, codeine	Clinically ineffective
• Ibuprofen	Other	• Acetaminophen
• Naproxen	• Butorphanol (IM)	• Chlorpromazine (IM)
• Butorphanol (IN)	• Chlorpromazine (IM, IV)	• Lidocaine (IV)
• Prochlorperazine (IV)	• Isometheptene	Unknown benefit
Migraine specific	• Ketorolac	• Dexamethasone (IV)
• Sumatriptan (SC, IN, PO)	• Ergotamine plus caffeine*	• Hydrocortisone (IV)
• Zolmitriptan	• Metoclopramide (IV)	
• Rizatriptan	• Naproxen (PO)	
• Naratriptan	• Prochlorperazine (IM, PR)	
• Almotriptan	• Lidocaine (IN)	
• Frovatriptan		
• Eletriptan		
• Dihydroergotamine (SC, IM, IN, IV)		

*Efficacy trials comparing ergotamine with placebo had mixed results. Strongest evidence for ergotamine efficacy was found in trials combining ergotamine with caffeine.
IN, intranasal; IV, intravenous; SC, subcutaneous; PO, orally; IM, intramuscular; PR, rectal.

Adapted with permission from the American Academy of Neurology. Quality Standards Subcommittee of the American Academy of Neurology, 2000, Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. Available at http:/www.aan.com/professionals/practice/pdfs/gl0087.pdf.

or combination modalities also play in reducing disability. The US Headache Consortium reported that relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and cognitive-behavioral therapy all appear to be modestly effective in preventing migraine (vs no treatment).[48] Behavioral therapy may be combined with preventive drug therapy to achieve additional clinical improvement for migraine relief. Preventive measures are not likely to prevent all migraine headaches, but may reduce the severity and/or duration of those that occur despite therapy. Finally, although evidence is limited, the Consortium suggests that acupuncture, TENS, cervical manipulation, occlusal adjustment, hypnosis, and hyperbaric oxygen treatments may also afford some benefit.[49]

Dysmenorrhea

Dysmenorrhea, or severe cramping pain in the lower abdomen (or lower back and/or upper thighs) occurring just prior to or during menses, affects approximately 72% of menstruating women.[50] In most younger women, dysmenorrhea is not associated with pelvic pathology, but is related to the release of prostaglandins F_2 and E_2 from the endometrium and the release of vasopressin during menses.[51] It may have a genetic component as well.[52] Pelvic pathology resulting in secondary dysmenorrhea is more common in women 20 years of age or older.[52] It is difficult to differentiate primary and secondary dysmenorrhea based on symptoms alone; pain symptoms have a similar onset (1 to 2 days prior to menses) and duration (48 to 72 hours). Pain that becomes progressively worse may be indicative of endometriosis. Treatment strategies for primary and secondary dysmenorrhea are different; therefore, it is important that patients discuss their symptoms with their healthcare providers in order to have them properly evaluated.

Oral contraceptives (OCs) are the mainstay of therapy for primary dysmenorrhea.[51,53] Because they suppress ovulation, OCs reduce the levels of prostaglandins that stimulate uterine activity and produce pain. Nonselective NSAIDs are highly effective (72% of women participating in 51 clinical trials achieved significant pain relief versus 15% of women treated with placebo)[54] and are commonly used to relieve the symptoms of primary dysmenorrhea. However, because they are nonselective, they also have GI and hematologic effects.

The COX-2–selective NSAID celecoxib is approved for the treatment of primary dysmenorrhea, but is only available by prescription. However, clinicians may want to consider reserving its use for patients at high risk of GI side effects, with no or low risk of CV disease.

Calcium channel blockers, such as nifedipine, can decrease uterine motility and reduce pain,[55] but generally are not considered good choices for young women because of their other effects. Alternative approaches to treating primary dysmenorrhea include TENS, acupuncture, and topical heat, all of which have demonstrated some utility.[56-59] Surgical procedures are a last resort in primary dysmenorrhea.

Summary

Given the many different types of pain, their etiologies, and accompanying comorbidities, the management of patients with painful conditions requires a balanced approach to treatment that encourages the utilization of disease-appropriate pharmacologic and nonpharmacologic modalities. Other considerations when selecting a course of therapy are age-related issues regarding proper pain management, pharmacokinetic issues, and the presence of risk factors for GI, liver, CV, or cardiorenal disease.

REFERENCES

1. Cherry DK, Woodwell DA. National Ambulatory Medical Care Survey: 2000 summary. Number 328. National Center for Health Statistics. Available at: http://www.cdc.gov/nchs/data/ad/ad328.pdf. Accessed June 1, 2004.
2. Leadbetter WB. Cell-matrix response in tendon injury. *Clin Sports Med.* 1992;11:533-578.
3. Best TM, Hunter KD. Muscle injury and repair. *Phys Med Rehabil Clin North Am.* 2000;11:251-266.
4. Elder CL, Dahners LE, Weinhold PS. A cyclooxygenase-2 inhibitor impairs ligament healing in the rat. *Am J Sports Med.* 2001;29:801-805.
5. Stovitz SD, Johnson RJ. NSAIDs and musculoskeletal treatment: what is the clinical evidence? *Phys Sportsmed.* 2003;31:35-40.
6. Almekinders LC, Temple JD. Etiology, diagnosis, and treatment of tendonitis: an analysis of the literature. *Med Sci Sports Exerc.* 1998;30:1183-1190.
7. Khan KM, Cook JL, Bonar F, Harcourt P, Astrom M. Histopathology of common tendinopathies: update and implications for clinical management. *Sports Med.* 1999;27:393-408.
8. Astrom M, Rausing A. Chronic Achilles tendinopathy: a survey of surgical and histopathologic findings. *Clin Orthop.* 1995;316:151-164.
9. Khan KM, Cook JL, Taunton JE, Bonar F. Overuse tendinosis, not tendinitis. Part 1: a new paradigm for a difficult clinical problem. *Phys Sportsmed.* 2000;28:38-48.
10. Uhthoff HK, Sano H. Pathology of failure of the rotator cuff tendon. *Orthop Clin North Am.* 1997;28:31-41.
11. Alfredson H, Pietila T, Jonsson P, Lorentzon R. Heavy-load eccentric calf muscle training for the treatment of chronic Achilles tendinosis. *Am J Sports Med.* 1998;26:360-366.
12. Mafi N, Lorentzon R, Alfredson H. Superior short-term results with eccentric calf muscle training compared to concentric training in a randomized prospective multicenter study on patients with chronic Achilles tendinosis. *Knee Surg Sports Traumatol Arthrosc.* 2001;9:42-47.
13. Almekinders LC. Anti-inflammatory treatment of muscular injuries in sport: an update of recent studies. *Sports Med.* 1999;28:383-388.
14. Reynolds JF, Noakes TD, Schwellnus MP, Windt A, Bowerbank P. Non-steroidal anti-inflammatory drugs fail to enhance healing of acute hamstring injuries treated with physiotherapy. *S Afr Med J.* 1995;85:517-522.
15. Beiner JM, Jokl P. Muscle contusion injuries: current treatment options. *J Am Acad Orthop Surg.* 2001;9:227-237.
16. van Staa TP, Leufkens HG, Cooper C. Use of nonsteroidal anti-inflammatory drugs and risk of fractures. *Bone.* 2000;27:563-568.
17. Giannoudis PV, MacDonald DA, Matthews SJ, Smith RM, Furlong AJ, De Boer P. Nonunion of the femoral diaphysis: the influence of reaming and non-steroidal anti-inflammatory drugs. *J Bone Joint Surg (Br).* 2000;82:655-658.
18. Rosomoff HL, Rosomoff RS. Low back pain. Evaluation and management in the primary care setting. *Med Clin North Am.* 1999;83:643-662.
19. Turk DC. Treatment of chronic pain: clinical outcomes, cost-effectiveness, and cost benefits. *Drug Benefit Trends.* 2001;13:36-38.
20. Andersson GB. Epidemiological features of chronic low-back pain. *Lancet.* 1999;354:581-585.
21. Deyo RA, Weinstein JN. Low back pain. *N Engl J Med.* 2001;344:363-370.
22. Bigos SJ, Bowyer OR, Braen GR, et al. Acute low back problems in adults. Clinical practice guidelines no. 14. AHCPR publication no. 95-0642. Agency for Health Care Policy and Research. Available at: http://hstat.nlm.nih.gov/hq/Hquest/db/local.arahcpr.arclin.lbpc/screen/TocDisplay/da/1/s/33866/action/Toc;jsessionid=80ABC51802E0A6462657290FE057DF21. Accessed February 23, 2004.
23. Philadelphia Panel. Philadelphia Panel evidence-based clinical practice guidelines on selected rehabilitation interventions for low back pain. *Phys Ther.* 2001;81:1641-1674.
24. Hides JA, Jull GA, Richardson CA. Long-term effects of specific stabilizing exercises for first-episode low back pain. *Spine.* 2001;26:E243-E248.
25. Atkinson JH, Slater MA, Williams RA, et al. A placebo-controlled randomized clinical trial of nortriptyline for chronic low back pain. *Pain.* 1998;76:287-296.
26. Ward NG. Tricyclic antidepressants for chronic low-back pain. Mechanisms of action and predictors of response. *Spine.* 1986;11:661-665.
27. van Tulder MW, Scholten RJ, Koes BW, Deyo RA. Nonsteroidal anti-inflammatory drugs for low back pain: a systematic review within the framework of the Cochrane Collaboration Back Review Group. *Spine.* 2000;25:2501-2513.
28. Hillis WS. Areas of emerging interest in analgesia: cardiovascular complications. *Am J Ther.* 2002;9:259-269.
29. Whelton A. Renal effects of over-the-counter analgesics. *J Clin Pharmacol.* 1995;35:454-463.
30. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol.* 1999;26(suppl 56):18-24.
31. Browning R, Jackson JL, O'Malley PG. Cyclobenzaprine and back pain: a meta-analysis. *Arch Intern Med.* 2001;161:1613-1620.
32. Borenstein DG, Korn S. Efficacy of a low-dose regimen of cyclobenzaprine hydrochloride in acute skeletal muscle spasm: results of two placebo-controlled trials. *Clin Ther.* 2003;25:1056-1073.
33. Cherkin DC, Wheeler KJ, Barlow W, Deyo RA. Medication use for low back pain in primary care. *Spine*. 1998;23:607-614.
34. Jamison RN, Raymond SA, Slawsby EA, Nedeljkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. A randomized prospective study. *Spine.* 1998;23:2591-2600.
35. Nelemans PJ, deBie RA, deVet HC, Sturmans F. Injection therapy for subacute and chronic benign low back pain. *Spine.* 2001;26:501-515.
36. Moreland LW, St Clair EW. The use of analgesics in the management of pain in rheumatic diseases. *Rheum Dis Clin North Am*. 1999;25:153-191.
37. Schnitzer TJ, Gray WL, Paster RZ, Kamin M. Efficacy of tramadol in treatment of chronic low back pain. *J Rheumatol.* 2000;27:772-778.
38. Katz WA. Pharmacology and clinical experience with tramadol in osteoarthritis. *Drugs*. 1996;52(suppl 3):39-47.
39. Welch KM. Contemporary concepts of migraine pathogenesis. *Neurology.* 2003;61(8 suppl 4):S2-S8.
40. International Headache Society. International classification of headache disorders. *Cephalalgia.* 2004;24(suppl 1):1-151. Available at: http://216.25.100.131/ihscommon/guidelines/pdfs/full/_form_watermarked.pdf. Accessed June 28, 2005.
41. Lipton RB, Stewart WF. Migraine in the United States: a review of epidemiology and health care use. *Neurology.* 1993;43(6 suppl 3):S6-S10.
42. Schwartz BS, Stewart WF, Simon D, Lipton RB. Epidemiology of tension-type headache. *JAMA*. 1998;279:381-383.
43. Scher AI, Stewart WF, Liberman J, Lipton RB. Prevalence of frequent headache in a population sample. *Headache.* 1998;38:497-506.
44. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache*. 2001;41:646-657.
45. Ramadan NM, Silberstein SD, Freitag FG, Gilbert TT, Frishberg BM. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management for prevention of migraine. Available at: http://www.aan.com/professionals/practice/pdfs/g10090.pdf. Accessed December 9, 2003.
46. Matchar DB, Young WB, Rosenberg JH, et al. Evidence-based guidelines for migraine headache in the primary care setting: pharmacological management of acute attacks. Available at: http://www.aan.com/professionals/practice/pdfs/gl0087.pdf. Accessed December 9, 2003.
47. Lipton RB, Baggish JS, Stewart WF, et al. Efficacy and safety of acetaminophen in the treatment of migraine: results of a randomized, double-blind, placebo-controlled, population-based study. *Arch Intern Med.* 2000; 160:3486-3492.
48. Campbell JK, Penzien DB, Wall EM. Evidence-based guidelines for migraine headache: behavioral and physical treatments. Available at: http://www.aan.com/professionals/practice/pdfs/gl0089.pdf. Accessed December 9, 2003.
49. Silberstein SD, for the US Headache Consortium. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2000;55:754-762.
50. Andersch B, Milsom I. An epidemiologic study of young women with dysmenorrhea. *Am J Obstet Gynecol.* 1982;144:655-660.
51. Dawood MY. Dysmenorrhea. *Clin Obstet Gynecol.* 1990;33:168-178.
52. El-Minawi AM, Howard FM. Dysmenorrhea. In: Howard FM, Perry CP, Carter JE, El-Minawi AM, Li R-Z, eds. *Pelvic Pain: Diagnosis and Management.* Philadelphia, Pa: Lippincott Williams and Wilkins; 2000:100-107.
53. Chan WY, Dawood MY, Fuchs F. Prostaglandins in primary dysmenorrhea. Comparison of prophylactic and nonprophylactic treatment with ibuprofen and use of oral contraceptives. *Am J Med.* 1981;70:535-541.
54. Owen PR. Prostaglandin synthetase inhibitors in the treatment of primary dysmenorrhea. Outcome trials reviewed. *Am J Obstet Gynecol.* 1984;148:96-103.
55. Andersson KE, Ulmsten U. Effects of nifedipine on myometrial activity and lower abdominal pain in women with primary dysmenorrhoea. *Br J Obstet Gynaecol.* 1978;85:142-148.
56. Akin MD, Weingand KW, Hengehold DA, Goodale MB, Hinkle RT, Smith RP. Continuous low-level topical heat in the treatment of dysmenorrhea. *Obstet Gynecol.* 2001;97:343-349.
57. Kaplan B, Peled Y, Pardo J, et al. Transcutaneous electrical nerve stimulation (TENS) as a relief for dysmenorrhea. *Clin Exp Obstet Gynecol.* 1994;21:87-90.
58. Milsom I, Hedner N, Mannheimer C. A comparative study of the effect of high-intensity transcutaneous nerve stimulation and oral naproxen on intrauterine pressure and menstrual pain in patients with primary dysmenorrhea. *Am J Obstet Gynecol.* 1994;170:123-129.
59. Beal MW. Acupuncture and acupressure. Applications to women's reproductive health care. *J Nurse Midwifery.* 1999;44:217-230.

PATIENT CONSIDERATIONS: SPECIAL POPULATIONS

Daniel O. Clegg, MD
Professor of Medicine
Division of Rheumatology
University of Utah School of Medicine
Salt Lake City, Utah

J. Michael Gaziano, MD, MPH
Chief, Division of Aging
Brigham and Women's Hospital
Director, MAVERIC and GRECC,
VA Boston Healthcare System
Associate Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Richard C. Dart, MD, PhD
Director, Rocky Mountain Poison and
Drug Center, Denver Health
Professor of Surgery
(Emergency Medicine)
University of Colorado
Health Sciences Center
Denver, Colorado

Byron Cryer, MD
Associate Professor of Internal Medicine
University of Texas
Southwestern Medical Center
Dallas, Texas

Deborah S. Litman, MD, FACR
Clinical Assistant Professor of Medicine
Georgetown University
Washington, District of Columbia

INTRODUCTION

Certain patient populations, such as the elderly, patients at risk for gastrointestinal (GI) bleeding, patients with liver disease, patients with cardiovascular (CV) disease, and patients taking other medications, can present unique challenges to the management of pain. Treatment strategies for these patients may differ from those for healthy, younger adults. Further complicating the issue is that various pain therapies have been associated with undesirable side effects that may negatively impact patient outcomes. This article reviews some of the common pain-management issues in special populations that are likely to confront clinicians.

Pain in the Elderly

Elderly patients often have multiple medical problems and many potential sources of pain. Because pain can be both a cause and a result of medical conditions in this population, optimum patient care depends on understanding its role and including pain control as part of disease management. The results of 3 randomized, controlled trials demonstrated that disease and pain management could be improved by specific interventions in the long-term care and outpatient settings.[1-3] The results suggest that better overall care of older patients requires improved recognition and management of pain.

In the United States, antipsychotic medications are used by more than 20% of long-term-care residents to control a variety of behavioral symptoms, primarily those resulting from dementia.[4] Based on the hypothesis that poor pain control can increase disruptive behavior, investigators implemented a comprehensive program to reduce antipsychotic medication use through education of physicians, nurses, and other nursing-home staff.[1] Results showed that the number of days of antipsychotic medication use declined significantly (by 23%, P=.014) in the facilities in which the plan was implemented, and no increases in behavioral problems were observed.

Falls create a substantial burden for patients and for facilities, including excess medical treatment, surgery, and deaths. Risk factors include both endogenous (eg, functional impairment) and exogenous factors (eg, environmental hazards, all forms of drug use). Pain is also a risk factor for falling in nursing homes. For example, pain can cause physical instability, which increases the risk of falling. In addition, inadequate pain management can lead to disruptive behaviors and difficulty sleeping—this can result in the unnecessary use of antipsychotic medications and sleep aids, which are, in turn, associated with functional impairment and falls. Therefore, even if pain does not appear to be a primary problem, it contributes to a patient's overall condition. In facilities in which consultation was undertaken to assess and alter environmental and personal safety, recurrent falls were reduced significantly (P=.03).[2]

Patients With GI Complications

Among the analgesics used commonly for mild-to-moderate pain, nonsteroidal anti-inflammatory drugs (NSAIDs) as a class are associated with GI bleeding, which is related to cyclooxygenase (COX) inhibition and reduction of gastroprotective prostaglandins, direct deleterious effects on the gastric mucosa, and the inhibition of platelet aggregation.[5] NSAIDs include nonsalicylates (eg, ibuprofen, diclofenac), salicylates (eg, aspirin), and COX-2–selective NSAIDs (eg, celecoxib). These agents do not carry equal degrees of risk with regard to GI toxicity. The prescription COX-2 inhibitors are thought to have improved GI safety profiles because of their purported selective effects; however, like the nonselective NSAIDs, COX-2 inhibitors can cause edema and aggravate hypertension and should be used with caution in patients with underlying CV disease.[6]

A number of risk factors for developing serious GI complications have been established (Figure 1).[7-11] The most common are advanced age, history of upper GI problems, higher NSAID doses, multiple

NSAID use, and concomitant use of other medications, such as prednisone. Based on available data, it is clear that NSAIDs, including over-the-counter (OTC) agents, are associated with both upper and lower GI risks. Aspirin contributes substantially to the risk, even when it is used occasionally or at low doses.[12-14] In a cohort study, the risk of GI bleeding in a population taking low doses (100 or 150 mg/d) of aspirin was increased over the general population by a factor of 2.6 (95% confidence interval [CI], 2.2-2.9). For low-dose aspirin combined with NSAIDs, the risk was increased 5.6-fold (95% CI, 4.4-7.0).[15] Acetaminophen, because it has a minimal effect on prostaglandin synthesis, is not associated with negative GI effects.[16]

The prescription COX-2 inhibitors were believed to have improved GI safety profiles; however, only rofecoxib has clearly established a proven GI benefit.[17] The Celecoxib Long-term Arthritis Safety Study (CLASS) demonstrated that, at 6 months, celecoxib was associated with a lower incidence of combined upper GI ulcer complications and symptomatic ulcers than were ibuprofen and diclofenac.[18] However, the concomitant use of aspirin negated the difference between celecoxib and the comparator agents. Furthermore, at 12-month follow-up, there was no clear difference in GI symptoms among the agents.[19]

Enteric coating and buffering do not reduce risks associated with aspirin.[14,15] These effects are important because of the widespread use of these agents and because of the increased risk when even low-dose aspirin is combined with other NSAIDs. When prescribing NSAIDs or aspirin, healthcare providers should monitor patients carefully, especially those at high risk for GI complications, such as the elderly, and counsel them not to exceed recommended doses. If GI symptoms develop, patients can be switched to acetaminophen, or an antacid or antisecretory agent (eg, proton pump inhibitor, histamine H_2-receptor agonist) can be added to the regimen.[20]

In order to reduce the risk of GI complications, acetaminophen can be considered a first-line agent for the treatment of mild-to-moderate pain in patients at risk for GI complications. The existing evidence indicates that recommended dosages (≤4000 mg/d) of acetaminophen do not cause GI irritation, erosions, bleeding, or ulcers and that acetaminophen can be recommended safely as an alternative to aspirin or nonaspirin NSAIDs.[21-24]

Analgesics for Patients With a History of Liver Disease

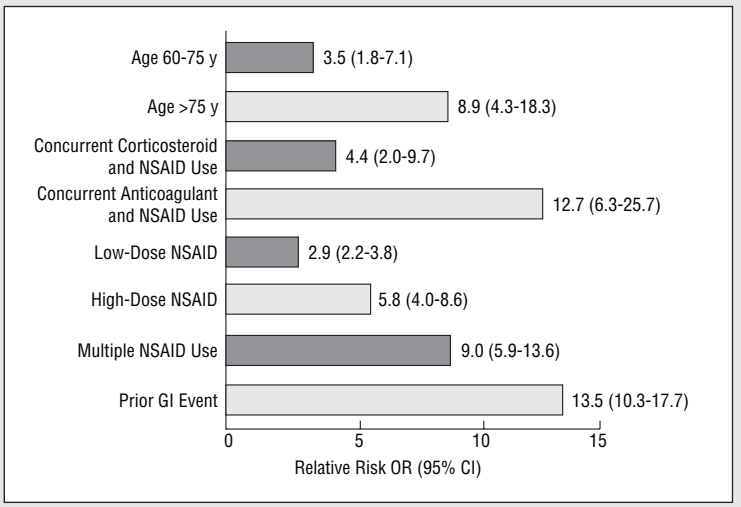
The use of analgesics in patients with liver disease or those who use more than a moderate amount of alcohol regularly is a subject of some controversy and ongoing investigation. Acetaminophen is used frequently to treat mild-to-moderate pain in patients with liver disease because they are at risk for upper GI hemorrhage. Because a large overdose of acetaminophen can lead to hepatotoxicity, some have speculated that patients with compromised liver function—for example, those with a history of liver disease or alcohol abuse—may be at increased risk when using acetaminophen. The data, however, do not support this conclusion.

Acetaminophen is metabolized primarily in the liver by glucuronidation, sulfation, and oxidation, with a small percentage of the recommended dose excreted unchanged in the urine. Approximately one half to one third is conjugated with glucuronide and one fourth to one third with sulfate; both reactions form nontoxic metabolites that are eliminated in the bile or excreted in the urine. Less than 10% is metabolized by cytochrome P4502E1 (CYP2E1) to form the highly reactive intermediate *N*-acetyl-*p*-benzoquinone imine, which is almost instantaneously deactivated by hepatocellular stores of glutathione to form nontoxic cysteine and mercapturic conjugates (Figure 2, page 22).[25] Based on this pattern, factors that induce CYP2E1 activity and/or reduce hepatic glutathione stores significantly could theoretically increase the risk for acute liver damage.

Chronic liver disease, however, does not cause glutathione deficiency, nor does it shift metabolism

Figure 1

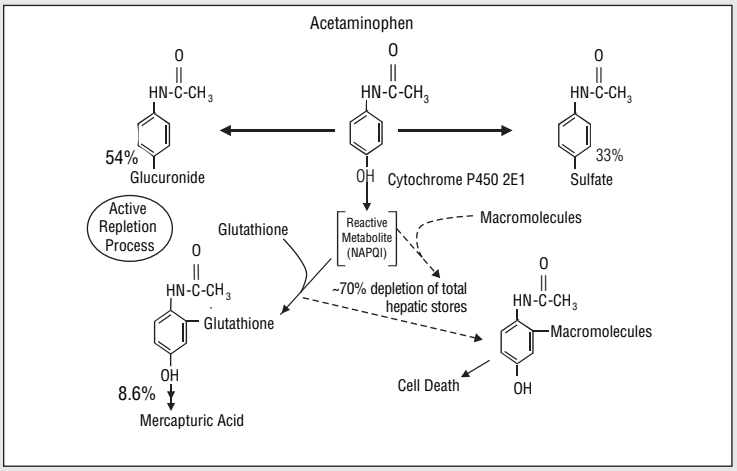
RISK FACTORS FOR SERIOUS GI ADVERSE EVENTS: RELATIVE RISKS[7-11]



GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; CI, confidence interval.

Figure 2

ACETAMINOPHEN METABOLISM[25]



The majority of acetaminophen is metabolized by the liver via glucuronidation and sulfation to nontoxic metabolites. Less than 10% of acetaminophen is metabolized by CYP2E1, which converts acetaminophen to *N*-acetyl-*p*-benzoquinone imine (NAPQI), the toxic intermediate metabolite. NAPQI is rapidly detoxified by hepatic glutathione and excreted in the urine.

Reprinted with permission from Benson GD et al. *Am J Ther.* 2005;12:133-141.

to the oxidative pathway.[26] Furthermore, acetaminophen given at 4000 mg/d is well tolerated in patients with stable chronic liver disease.[27] It does not appear to affect alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, nor does it accumulate in serum or tissues beyond normal levels.[27,28] A recent article by Benson and colleagues concluded that acetaminophen can be used safely in patients with liver disease and is a preferred analgesic/antipyretic because of the absence of platelet impairment, GI toxicity, and nephrotoxicity associated with NSAIDs.[25]

Alcohol

A systematic review by Dart and colleagues identified articles that pertained to the use of recommended dosages (≤4000 mg/d) of acetaminophen by adult alcoholic patients.[29] Each article was classified according to its methodology, using a common classification system. There were 2 class I studies (controlled, randomized, and blinded clinical trials), 5 class II studies (prospective, nonrandomized, or nonblinded clinical trials, cohort or well-designed case-control studies, dramatic results in uncontrolled studies, and volunteer studies), and 25 patients in 20 class III studies (retrospective case series, case reports).

Class I and II data demonstrated little if any risk of liver injury in alcoholic patients who ingest a recommended dosage (≤4000 mg/d) of acetaminophen. Only class III data described an association of therapeutic acetaminophen ingestion with liver injury in alcoholic patients.[29] However, these class III studies reported on retrospective data that are based exclusively on patient histories, which are often incomplete and occasionally conflicting; these include probable inaccuracies in the patient's history, especially with respect to the dose of acetaminophen ingested, and serum acetaminophen levels that are more consistent with acute overdose than recommended dosing.

Although aspirin and nonaspirin NSAIDs are not contraindicated in alcoholics, available data suggest that they should be used with caution in patients who consume alcohol regularly, and their use should be carefully monitored because of concerns regarding GI bleeding. In an interview-based case-control study of 1224 patients hospitalized for acute major upper GI bleeding and 2945 neighbor controls, the risk for upper GI bleeding increased with higher alcohol consumption in the entire study population, with relative risks (95% CI) of 0.9 (0.8-1.2), 1.3 (1.0-1.7), 1.4 (1.0-2.0), and 2.8 (2.0-3.9) for 1 to 6 drinks/week, 7 to 13 drinks/week, 14 to 20 drinks/week, and ≥21 drinks/week, respectively, compared with 1 drink/week.[13] Among regular aspirin users (use at least every other day the week prior to the event), any level of drinking increased the risk for acute major upper GI bleeding (multivariate relative risk [MVRR], 2.8; 95% CI, 2.1-3.8, and MVRR, 7.0; 95% CI, 5.2-9.3, for regular users of (≤325 mg and >325 mg, respectively). Among current drinkers, even occasional aspirin use was associated with increased risk for upper GI bleeding (MVRR, 2.4; 95% CI, 1.9-3.0) at all levels. In a separate mail survey conducted by the American College of Gastroenterology, drinking (level not described) was associated with a 2-fold increased risk for GI bleeding that appeared to be at least additive to that associated with recent NSAID use.[16]

Available data from prospective studies indicate that recommended dosages (≤4000 mg/d) of acetaminophen may be taken by alcoholic patients without added risk of liver injury.[29,30] Chronic heavy alcohol abusers may have an increased risk of hepatotoxicity following an overdose of acetaminophen,[29] and patients should be cautioned not to exceed the recommended dose. It should also be noted that the US Food and Drug Administration (FDA) requires that all OTC analgesics carry an alcohol warning that advises patients who consume 3 or more alcoholic drinks every day to consult their clinician.

Patients With Underlying CV Disease

The use of analgesics in patients with underlying CV disease has been complicated by the recent

withdrawal of two COX-2 inhibitors, rofecoxib and valdecoxib, from the market because of concerns about their CV event profiles and the subsequent report that celecoxib may also be associated with negative CV effects.[31]

Moreover, recent data from ADAPT (Arthritis, Diet and Activity Promotion Trial) indicated an apparent increase in CV and cerebrovascular events among patients taking naproxen compared to those taking placebo.[32] As this is the first study to show that naproxen may increase the risk of heart attack or stroke and because other studies have supported a modest degree of cardioprotection with naproxen, it seems premature to judge any possible untoward CV effect of naproxen.[33] However, the agent's labeling recommends that naproxen be used for no more than 10 days.[34]

These reports and the findings from the Arthritis and Drug Safety Advisory Committees prompted FDA to ask the manufacturers of all prescription NSAIDs to revise their labeling to include a boxed warning highlighting the potential for increased risk of CV and GI adverse events associated with their use (Table 1). Manufacturers of celecoxib and all other prescription NSAIDs have been asked to revise their labeling to include a Medication Guide for patients to help make them aware of the potential for CV and GI adverse events associated with the use of this class of drugs.

In addition, FDA is asking the manufacturers of all OTC NSAIDs to revise their labels to include more specific information about potential CV and GI risks, along with information to assist consumers in the safe use of the drugs. FDA is also asking manufacturers of OTC NSAIDs to include a warning about the risk of potential skin reactions. The labeling of prescription NSAIDs already addresses potential skin reactions.[35]

These FDA-mandated changes highlight the need for greater scrutiny of all NSAIDs. With this in mind, the following stepwise approach to pain management has been proposed.[36] Acetaminophen, which is not associated with significant CV or cardiorenal effects,[37,38] is recommended as the first-line agent for mild-to-moderate pain. Ibuprofen is recommended for those patients who do not respond to the maximum recommended dose (4000 mg/d) of acetaminophen, and who are not at risk for heart disease,[37] kidney disease,[38] or GI side effects.[39] Although COX-2 inhibitors remain a rational choice for patients at high risk for GI events who are at low risk for CV events, it would seem sensible to avoid prescribing these agents to patients who have or are at risk for CV events until further long-term studies are complete.

Table 1

NSAID BLACK BOX WARNINGS

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
- [Drug Name] is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery.

Gastrointestinal Risk

- NSAIDs may cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.

NSAID, nonsteroidal anti-inflammatory drug.

Analgesics for Patients With Other Risk Factors

In healthy patients, the risk of developing renal failure with OTC analgesics (aspirin, nonaspirin NSAIDs, or acetaminophen) is minimal.[40] The Physicians' Health Study (PHS)—a prospective study in a cohort of 11,032 apparently healthy male physicians—reviewed the use of OTC analgesics (aspirin, nonaspirin NSAIDs, or acetaminophen) over a period of 14 years and found these agents were not associated with renal toxicity (defined as increased serum creatinine/reduced creatinine clearance levels).[40]

Patients with hypertension, severe renal insufficiency, congestive heart failure, or other disorders of salt and water retention should be reminded of the risk of analgesic use. Patients with these conditions are likely to rely more heavily on renal prostaglandins to maintain normal renal blood flow and function than do otherwise healthy individuals.[41]

Inhibition of prostaglandin synthesis in such patients can reduce renal blood flow and glomerular filtration rate (resulting in increased blood urea nitrogen and creatinine levels), increase chloride absorption and sodium retention (resulting in edema and hypertension), reduce renin and aldosterone activity (resulting in elevated potassium levels), and increase the effect of antidiuretic hormone (resulting in water retention and hypervolemia).

The mechanisms of action of NSAIDs suggest that they could influence salt and water retention and

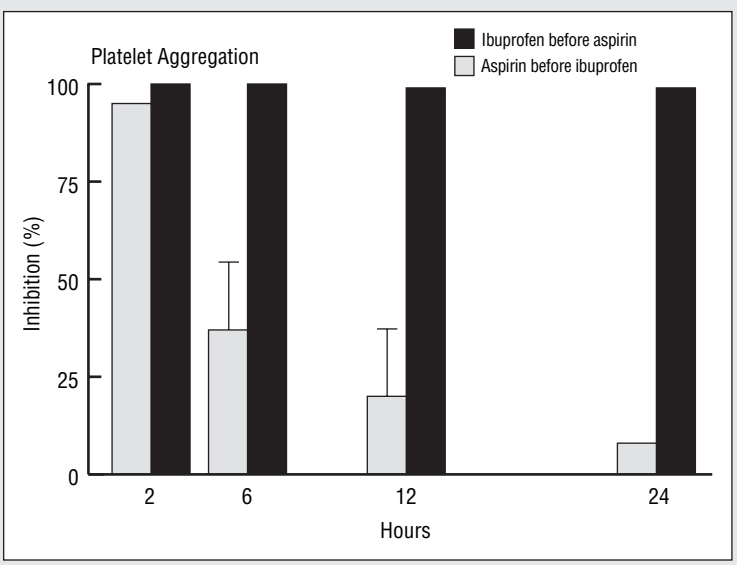
hypertension.[41] In meta-analyses, increases in blood pressure occurred in patients with hypertension using NSAIDs, including those on treatment.[42] In one analysis, indomethacin and naproxen were associated with the greatest increases in blood pressure.[43] A multicenter, randomized, controlled trial indicated that both celecoxib and rofecoxib were associated with the development of edema and hypertension.[6] Acetaminophen does not affect the function of the kidneys or heart and can be used as an alternative in these patients.

Aspirin

Some reports suggest that NSAIDs can negate the cardioprotective effects of aspirin. A randomized study by Catella-Lawson and colleagues was undertaken to determine whether the antiplatelet effects of low-dose aspirin would be affected by the concomitant use of common pain medications including ibuprofen, rofecoxib, diclofenac, and acetaminophen.[44] Results demonstrated that inhibition of serum thromboxane B_2 formation and platelet aggregation were blocked when a single daily dose of ibuprofen was given before aspirin (Figure 3).[44] The same held true when multiple doses were given. However, the concomitant administration of acetaminophen, rofecoxib, or diclofenac did not affect the pharmacodynamics of aspirin. Researchers concluded the concomitant use of ibuprofen antagonizes the irreversible platelet inhibition induced by aspirin.[44]

Figure 3

EFFECTS OF IBUPROFEN ON THE CARDIOPROTECTIVE EFFECTS OF LOW-DOSE ASPIRIN[44]



At 24 hours, mean degree of platelet aggregation inhibition was 98 ± 1% when aspirin was given before ibuprofen, but 2 ± 1% when ibuprofen was given before aspirin (P<.001).

In a noncontrolled study by MacDonald and Wei, patients taking low-dose aspirin (≤325 mg/d) for secondary prevention of CV disease and concomitant ibuprofen had an almost 2-fold increased risk for all-cause mortality. When compared to patients taking low-dose aspirin alone, there was a more than 70% increased risk for CV mortality compared to aspirin plus other NSAIDs.[45]

Further evidence of the impact of NSAIDs when taken concomitantly with aspirin was demonstrated in a recent case-control study that evaluated the effects of OTC and prescription NSAID use on CV events, both alone and in combination with aspirin.[46] Results showed that the use of either aspirin or NSAIDs alone was associated with a reduced risk of myocardial infarction (MI), but that when combined with NSAIDs, aspirin exerted no cardioprotective effects (odds ratio, 1.28). For patients classified as frequent users of NSAIDs, aspirin users had a higher risk of MI than did nonaspirin users. Much of this effect seemed to be ibuprofen related, reinforcing the impression that there are differences in the interactions with various NSAIDs.

A subgroup analysis from the PHS provides some additional data on the primary cardioprotective effects of aspirin and the concomitant use of NSAIDs in general.[47] This study randomized 22,071 apparently healthy male physicians to 325 mg aspirin or placebo on alternating days. Investigators then prospectively collected data on medical condition, compliance, and concomitant NSAID use. NSAID use in addition to aspirin/placebo was categorized as never, intermittent (1-59 days/year), or regular (≥60 days/year). During a follow-up period that averaged 5 years, the study findings demonstrated a highly significant 44% reduction in the risk of first MI with aspirin (P<.00001) as compared to placebo. Intermittent use of NSAIDs had no material effect on aspirin's cardioprotective effect; however, in those who took NSAIDs 60 days or more per year, there was no protective effect of aspirin use. This interference could be the result of competitive interactions at the shared docking site on COX-1.[47]

Aspirin Use in Women

Ridker and colleagues recently published the Women's Health Study (WHS), which assessed

whether the use of 100 mg of aspirin every other day decreases the risk of a first MI.[48] The results of this study were somewhat different from data that have been reported in men. The study reported only a 9% reduction in major CV events in the aspirin group vs placebo (*P*=.13). Furthermore, it was noted that there was no decrease in death from CV causes (*P*=.68). Aspirin had no statistically significant effect on the risk of fatal or nonfatal MI (*P*=.83). However, a subgroup analysis of women 65 years of age or older demonstrated a 34% reduction in first MI. When aspirin was compared to placebo, there was a 17% reduction in the risk of stroke (*P*=.04) and a 24% reduction in the risk of ischemic stroke (*P*=.009). In women 65 years of age or older, there was a 30% reduction in stroke.

The researchers noted that there are risks associated with aspirin therapy (eg, an increased risk of GI bleeds requiring transfusion in the aspirin group [*P*=.02] and a statistically insignificant increase in hemorrhagic stroke [*P*=.31]). The results of this study differ from those of the PHS and may be attributed to the different doses of aspirin given: 100 mg in the WHS vs 325 mg in the PHS. The difference in the gender of the subjects in the 2 trials also may be a factor.

Although chance, bias, and confounding factors remain possible alternate explanations, study data suggest that when low-dose aspirin is used with NSAIDs long term, there may be a reduced ability of aspirin to protect against CV disease.[49] Unlike NSAIDs, acetaminophen has not been shown to interfere with aspirin.[44] However, additional studies are needed in women, in larger numbers of patients, and with a variety of different NSAIDs.

Summary

This article suggests that many analgesics should be used cautiously in special populations. It is important to remember that all medications, including those that are available OTC, carry both risks and benefits. As with any pharmacologic agent, the risk of side effects must be balanced against the benefits. The reality is that many patients must continue to take analgesics over the long term. As clinicians consider how to counsel patients who take these medications, it is important to carefully evaluate each patient's relative-risk profile before prescribing or discontinuing therapy and to consider other analgesics with better established safety profiles, if appropriate. Patients should be reminded about the potential adverse events that are associated with therapy, the risks of exceeding recommended dosing schedules, and the potential for drug-drug interactions.

References

1. Meador KG, Taylor JA, Thapa PB, Fought RL, Ray WA. Predictors of antipsychotic withdrawal or dose reduction in a randomized controlled trial of provider education. *J Am Geriatr Soc.* 1997;45:207-210.
2. Ray WA, Taylor JA, Meador KG, et al. A randomized trial of a consultation service to reduce falls in nursing homes. *JAMA.* 1997;278:557-562.
3. Ray WA, Stein CM, Byrd V, et al. Educational program for physicians to reduce use of non-steroidal anti-inflammatory drugs among community-dwelling elderly persons: a randomized controlled trial. *Med Care.* 2001;39:425-435.
4. Ray WA, Taylor JA, Meador KG, et al. Reducing antipsychotic drug use in nursing homes. A controlled trial of provider education. *Arch Intern Med.* 1993;153:713-721.
5. Ivey KJ. Mechanisms of nonsteroidal anti-inflammatory drug-induced gastric damage: actions of therapeutic agents. *Am J Med.* 1988;84(suppl 2A):41-48.
6. Whelton A, Fort JG, Puma JA, Normandin D, Bello AE, Verburg KM, for the SUCCESS VI Study Group. Cyclooxygenase-2–specific inhibitors and cardiorenal function: a randomized, controlled trial of celecoxib and rofecoxib in older hypertensive osteoarthritis patients. *Am J Ther.* 2001;8:85-95.
7. Hansen JM, Hallas J, Lauritsen JM, Bytzer P. Non-steroidal anti-inflammatory drugs and ulcer complications: a risk factor analysis for clinical decision-making. *Scand J Gastroenterol.* 1996;31:126-130.
8. Gutthann SP, García Rodríguez LA, Raiford DS. Individual nonsteroidal antiinflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. *Epidemiology.* 1997;8:18-24.
9. García Rodríguez LA, Jick H. Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *Lancet.* 1994;343:769-772.
10. Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. *Arch Intern Med.* 1993;153:1665-1670.
11. Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. *Ann Intern Med.* 1991;114:735-740.
12. Weil J, Colin-Jones D, Langman M, et al. Prophylactic aspirin and risk of peptic ulcer bleeding. *BMJ.* 1995;310:827-830.
13. Kaufman DW, Kelly JP, Wiholm B-E, et al. The risk of acute major upper gastrointestinal bleeding among users of aspirin and ibuprofen at various levels of alcohol consumption. *Am J Gastroenterol.* 1999;94:3189-3196.
14. Kelly JP, Kaufman DW, Jurgelon JM, Sheehan J, Koff RS, Shapiro S. Risk of aspirin-associated major upper-gastrointestinal bleeding with enteric-coated or buffered product. *Lancet.* 1996;348:1413-1416.
15. Sørensen HT, Mellemkjaer L, Blot WJ, et al. Risk of upper gastrointestinal bleeding associated with use of low-dose aspirin. *Am J Gastroenterol.* 2000;95:2218-2224.
16. Blot WJ, McLaughlin JK. Over the counter non-steroidal anti-inflammatory drugs and risk of gastrointestinal bleeding. *J Epidemiol Biostat.* 2000;5:137-142.
17. Bombardier C, Laine L, Reicin A, et al, for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med.* 2000;343:1520-1528.
18. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA.* 2000;284:1247-1255.
19. Hrachovec JB, Mora M. Reporting of 6-month vs 12-month data in a clinical trial of celecoxib. *JAMA.* 2001;286:2398; author reply 2399-2400.
20. Fendrick AM. Developing an economic rationale for the use of selective COX-2 inhibitors for patients at risk for NSAID gastropathy. *Cleve Clin J Med.* 2002;69(suppl 1):SI-59–SI-64.
21. Laporte J-R, Carné X, Vidal X, Moreno V, Juan J, for the Catalan Countries Study on Upper Gastrointestinal Bleeding. Upper gastrointestinal bleeding in relation to previous use of analgesics and non-steroidal anti-inflammatory drugs. *Lancet.* 1991;337:85-89.
22. Johnson PC, Driscoll T. Comparison of plain and buffered aspirin with acetaminophen in regard to gastrointestinal bleeding. *Curr Ther Res.* 1981;30:79-84.

23. Hoftiezer JW, O'Laughlin JC, Ivey KJ. Effects of 24 hours of aspirin, Bufferin, paracetamol and placebo on normal human gastroduodenal mucosa. *Gut.* 1982;23:692-697.
24. McIntosh JH, Fung CS, Berry G, Piper DW. Smoking, nonsteroidal anti-inflammatory drugs, and acetaminophen in gastric ulcer: a study of associations and of the effects of previous diagnosis on exposure patterns. *Am J Epidemiol.* 1988;128:761-770.
25. Benson GD, Koff RS, Tolman KG. The therapeutic use of acetaminophen in patients with liver disease. *Am J Ther.* 2005;12:133-141.
26. Siegers C-P, Bossen KH, Younes M, Mahlke R, Oltmanns D. Glutathione and glutathione-S-transferases in the normal and diseased human liver. *Pharmacol Res Commun.* 1982;14:61-72.
27. Benson GD. Acetaminophen in chronic liver disease. *Clin Pharmacol Ther.* 1983;33:95-101.
28. Dargère S, Collet T, Crampon D, et al. Lack of toxicity of acetaminophen in patients with chronic hepatitis C: a randomized controlled trial. *Gastroenterology.* 2000;118. Abstract 222.
29. Dart RC, Kuffner EK, Rumack BH. Treatment of pain or fever with paracetamol (acetaminophen) in the alcoholic patient: a systematic review. *Am J Ther.* 2000;7:123-134.
30. Kuffner EK, Dart RC, Bogdan GM, Hill RE, Casper E, Darton L. Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med.* 2001;161:2247-2252.
31. National Institutes of Health. Questions and answers: NIH halts use of COX-2 inhibitor in large cancer prevention trial (press release, December 17, 2004). Available at: http://www.nih.gov/news/pr/dec2004/od-17Q&A.htm. Accessed January 11, 2005.
32. National Institutes of Health. Use of non-steroidal anti-inflammatory drugs suspended in large Alzheimer's disease prevention trial (press release, December 20, 2004). Available at: http://www.nih.gov/news/pr/dec2004/od-20.htm. Accessed February 14, 2005.
33. Topol EJ. Arthritis medicines and cardiovascular events—"house of coxibs." *JAMA.* 2005;293:366-368.
34. Aleve® tablets patient information. Available at: http://www.aleve.com/tablets.html. Accessed June 23, 2005.
35. Food and Drug Administration. FDA announces series of changes to the class of marketed non-steroidal anti-inflammatory drugs (NSAIDs). Available at: http://www.fda.gov/bbs/topics/news/2005/NEW01171.html. Accessed April 21, 2005.
36. DeNoon D. Vioxx fall no surprise to heart docs. Available at: http://my.webmd.com/content/Article/94/103039.htm. Accessed June 29, 2005.
37. Hillis WS. Areas of emerging interest in analgesia: cardiovascular complications. *Am J Ther.* 2002;9:259-269.
38. Whelton A. Renal effects of over-the-counter analgesics. *J Clin Pharmacol.* 1995;35:454-463.
39. Singh G, Triadafilopoulos G. Epidemiology of NSAID induced gastrointestinal complications. *J Rheumatol.* 1999;26(suppl 56):18-24.
40. Rexrode KM, Buring JE, Glynn RJ, Stampfer MJ, Youngman LD, Gaziano JM. Analgesic use and renal function in men. *JAMA.* 2001;286:315-321.
41. Whelton A. Renal and related cardiovascular effects of conventional and COX-2–specific NSAIDs and non-NSAID analgesics. *Am J Ther.* 2000;7:63-74.
42. Johnson AG. NSAIDs and blood pressure: clinical importance for older patients. *Drugs Aging.* 1998;12:17-27.
43. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. *Arch Intern Med.* 1993;153:477-484.
44. Catella-Lawson F, Reilly MP, Kapoor SC, et al. Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. *N Engl J Med.* 2001;345:1809-1817.
45. MacDonald TM, Wei L. Effect of ibuprofen on cardioprotective effect of aspirin. *Lancet.* 2003;361:573-574.
46. Kimmel SE, Berlin JA, Reilly M, et al. The effects of nonselective non-aspirin non-steroidal anti-inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. *J Am Coll Cardiol.* 2004;43:985-990.
47. Kurth T, Glynn RJ, Walker AM, et al. Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. *Circulation.* 2003;108:1191-1195.
48. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med.* 2005;352:1293-1304.
49. Horn JR, Hansten PD. Do NSAIDs impair the cardioprotective effects of aspirin? *Pharm Times.* 2004;70:104.

Posttest answer key

1.b 2.b 3.a 4.a 5.d 6.d 7.b 8.d 9.b 10.c 11.d 12.d 13.d 14.b 15.c 16.a 17.b 18.a 19.a 20.d

State-of-the-Art Management of Mild-to-Moderate Pain: Multimodal Management of Mild-to-Moderate Osteoarthritis, Musculoskeletal Pain, and Other Conditions

POSTTEST
SELF-ASSESSMENT/CME VERIFICATION

If you wish to receive CME credit and confirmation of your participation, please mail a photocopy of this completed form before August 31, 2006, to:

CME-UCHSC
4200 East 9th Avenue, #C295
Denver, CO 80262

Physician Assistants: Successful completion of the self-assessment is required to earn Category I (Preapproved) CME credit. Successful completion is defined as a cumulative score of at least 70% correct.

Instructions: For each of the questions or incomplete statements below, indicate the most appropriate response on the evaluation form on the next page.

1. On the numeric and visual analog scales, mild-to-moderate pain is defined as a score of:
   a. 2 to 4 b. 2 to 6
   c. 3 to 5 d. 3 to 6
2. In a study assessing physician practice styles, it was demonstrated that physicians spend more time on preventive services and encouraging active participation in care when patients are in pain.
   a. True b. False
3. Self-efficacy programs have demonstrated significant reductions in pain, and they are an important modality in multimodal pain management.
   a. True b. False
4. Characteristics of pain perception include all except which one of the following?
   a. Gender differences, which emerge at birth
   b. Ethnic differences
   c. Bidirectional effects of stress
5. When considering multimodal interventions for OA, first-line recommended pharmacotherapy is:
   a. Aspirin b. COX-2 inhibitors
   c. NSAIDs d. Acetaminophen
6. The primary mechanism of action of acetaminophen is:
   a. Inhibition of prostaglandins
   b. Stimulation of endorphins
   c. Receptor-mediated
   d. Unknown
7. In clinical trials, the Arthritis Self-Management Program has been shown to reduce pain significantly at 4 months, however, improvement diminishes after 20 months.
   a. True b. False
8. In a longitudinal study of 219 patients with low back pain, improved patient outcomes were the highest in which group(s)?
   a. NSAIDs
   b. Muscle relaxants
   c. Acetaminophen
   d. Combination of NSAIDs and muscle relaxants
   e. Combination of acetaminophen and muscle relaxants
9. Data suggest that patients with compromised liver function are at increased risk when using acetaminophen.
   a. True b. False
10. Which of the following statements is/are true?
    a. COX-2 inhibitors are associated with edema and hypertension.
    b. NSAIDs are associated with increased blood pressure.
    c. Both statements are true.
    d. Neither statement is true.
11. Which of the following statements is/are true?
    a. Risk factors for OA include female gender, increasing age, and obesity.
    b. There is not strong evidence supporting sodium hyaluronate injections in OA management.
    c. Physical therapy can diminish OA pain significantly.
    d. All of the above
    e. None of the above
12. In acute low back pain, recommended nonpharmacologic treatments include:
    a. Bedrest and traction
    b. TENS and biofeedback techniques
    c. Both a and b
    d. Neither a nor b
13. Which of the following statements is/are true?
    a. Eighty percent to 90% of back problems resolve within 3 months.
    b. Only 10% of patients with disk herniation have sufficient pain after 6 weeks that surgery is considered.
    c. Once back pain resolves, recurrences are rare.
    d. Both a and b
    e. Both a and c
14. Clinical evidence suggests that NSAIDs are of great benefit in DOMS.
    a. True b. False
15. First-line therapy for primary dysmenorrhea is:
    a. Calcium channel blockers b. NSAIDs
    c. Oral contraceptives d. Both a and c
16. Treatment of migraine is directed toward the underlying pathology, which is understood to be:
    a. Neurovascular b. Stress induced
    c. Vascular d. Neuropathic
17. NSAIDs have been proven to be more effective than physiotherapy and spinal manipulation in acute back pain.
    a. True b. False
18. At doses of 4000 mg/d or less, acetaminophen has not been shown to increase the risk of bleeding in patients with chronic liver disease or a history of alcohol intake.
    a. True b. False

19. Which of the following statements is false?
   a. Evidence-based analyses indicate that all analgesics can cause renal disease in a healthy population.
   b. Some evidence supports the view that NSAIDs can interfere with the cardioprotective effects of aspirin.
   c. The Women's Health Study demonstrated that aspirin had no statistically significant effect on the risk of fatal or nonfatal MI.
   d. The most common risk factors for developing serious GI complications are advanced age, history of GI problems, higher doses of NSAIDs, and concomitant use of other medications.

20. Which of the following statements is/are true?
   a. FDA has asked the manufacturers of all prescription NSAIDs to revise their labeling to include a boxed warning highlighting the potential for increased risk of CV events and GI bleeding.
   b. FDA has asked the manufacturers of all OTC NSAIDs to revise their labels to include more specific information about the potential CV and GI risks.
   c. FDA has asked the manufacturers of OTC NSAIDs to include a warning about the risk of potential skin reactions.
   d. All statements are true.

Please record your posttest answers:

1. _____ 2. _____ 3. _____ 4. _____ 5. _____ 6. _____ 7. _____ 8. _____ 9. _____ 10. _____

11. _____ 12. _____ 13. _____ 14. _____ 15. _____ 16. _____ 17. _____ 18. _____ 19. _____ 20. _____

Please see page 26 for the Answer Key.

REGISTRATION/EVALUATION FORM **Expiration Date to Receive Credit: August 31, 2006**

The University of Colorado School of Medicine would appreciate your comments regarding the quality of the information presented and thanks you for your participation.

	Strongly Agree	Agree	Disagree	Strongly Disagree
1. The program objectives were fully met.	a	b	c	d
2. The quality of the educational process (method of presentation and information provided) was satisfactory and appropriate.	a	b	c	d
3. The educational activity has enhanced my professional effectiveness and improved my ability to:				
A. Treat/manage patients	a	b	c	d
B. Communicate with patients	a	b	c	d
C. Manage my medical practice	a	b	c	d
4. The information presented was without promotional or commercial bias.	a	b	c	d
5. The program level was appropriate.	a	b	c	d

6. Suggestions regarding this material or recommendations for future presentations:

_____

_____

_____

I certify that I completed this CME activity. The actual amount of time I spent in this activity was: ____hour(s)____minutes.

_____
Signature

Name (Please print clearly.) _____ Degree_____

Specialty_____

Street Address_____

City_____State_____ZIP_____

Email_____Phone_____Fax_____

Editor, *CLINICIAN*®
SynerMed® Communications
Department MC54G
405 Trimmer Road
PO Box 458
Califon, NJ 07830

CME Materials Enclosed

Supplement to

CLINICIAN® **Vol. 23 No. 10**

STATE-OF-THE-ART MANAGEMENT OF MILD-TO-MODERATE PAIN

Multimodal Management of Mild-to-Moderate Osteoarthritis, Musculoskeletal Pain, and Other Conditions