PAIN MANAGEMENT

• Types of pain
• Prevalence and economic implications
• Guidelines for treatment
• Risk management
• Drug-delivery systems
• Pain in the elderly
• Multidisciplinary care

SPECIAL SUPPLEMENT TO MANAGED Care

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C hronic pain is a significant public health issue in the United States and an important concern for MCOs. Untreated or undertreated pain can evolve from a symptom to a chronic condition in its own right, one that has serious co-morbid, economic, and quality-of-life consequences. As understanding of the mechanisms involved in chronic pain increases, so too does the opportunity to manage affected patients in a cost-effective manner.

The purpose of this publication is to provide P&T committees with an understanding of options for addressing patients’ chronic pain. This peer-reviewed digest examines current guidelines for pain management, therapeutic approaches to care, and strategies for managing patients with various types of pain. In consolidating this information, it serves as a valuable tool for formulary committees and is an important contribution to the medical literature.
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Chronic pain is a significant public health issue and an important concern for MCOs. As our understanding of the mechanisms involved in chronic pain increases, so does the opportunity to manage patients cost-effectively. Appropriate pain management can improve overall patient care and quality of life, and reduce health care resource utilization.

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CHRISTOPHER L. EDWARDS, PhD

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Chronic pain is a significant public health issue in the United States and an important concern for MCOs. As our understanding of the mechanisms involved in chronic pain increases, so too does the opportunity to manage patients in a cost-effective manner. Appropriate pain management can positively affect overall patient care, improve quality of life, and reduce health care resource utilization.

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual and potential tissue damage, or described in terms of such damage” (IASP 1994). Although pain is a common, necessary experience to protect one from injury, when it impairs activities of daily living and persists for 3 months or longer — i.e., continues beyond the time required for tissue healing — it is generally considered to have become the disease of chronic pain.

Pain has become a significant public health concern in the United States. It is the most common reason that people seek medical care (Fox 2000). Pain is also the second leading cause of medically related work absenteeism, resulting in more than 50 million lost workdays each year (Fox 2000). Chronic pain in the general population ranges from 2 to 40 percent (Verhaak 1998), and at least 4 out of 10 people affected do not obtain adequate pain relief (Phillips 2000).

Chronic pain is especially significant for the elderly, many of whom also suffer from multiple medical comorbidities and who lack adequate social, emotional, and medical resources. It is likely that this issue will become an even greater concern as more and more members of the baby boom generation approach and surpass the age of 65 in the coming decades.

Chronic pain may be the most important, treatable symptom in patients with certain medical conditions like cancer and sickle cell disease, and with neurological diseases such as multiple sclerosis, chronic spondylolisthesis, neuropathy, and spinal cord disorders. Conversely, chronic pain may confound the treatment of many common medical conditions, such as hypertension and diabetes.

Beyond the medical treatments available, chronic pain has widespread biopsychosocial sequelae. It is associated with depression, social withdrawal, sleep disturbances, and impaired quality of life. Along with the pain experience itself, these concomitant conditions lead to...
decreased productivity and increased utilization of health care services, resulting in an estimated total annual cost to the U.S. economy of a staggering $85 to $90 billion (Gitlin 1999).

**CHRONIC PAIN AND MANAGED CARE**

Today, more than 90 percent of working Americans and nearly 5 million Medicare beneficiaries are enrolled in some form of MCO (Kaiser 2002). The number of Americans covered by managed care plans has made pain management a concern not only for the patients who suffer, but for MCOs as well. In the first comparative analysis of direct costs of common chronic conditions among adults in a managed care population, Fishman (1997) reported that chronic pain accounts for greater total annual costs than other chronic conditions, including heart disease, hypertension, and diabetes (Figure).

Thus, as noted by Joint Commission on Accreditation of Healthcare Organizations President Dennis S. O’Leary, MD, at a leadership summit on pain management sponsored by the Joint Commission and the American Pain Society, “Appropriate pain management is good medicine because it results in quicker clinical recovery, shorter hospital stays, fewer readmissions, and improved quality of life, leading to increased productivity.” He further noted that “the mystique of pain — the long-held notion that because pain is subjective, it eludes objective measurement — has given way to evidence-based medicine as newer methods of assessing and controlling pain have emerged” (Phillips 2000). The important implication made by these observations is that we no longer can ignore pain and expect it will reliably resolve, but should seek assessment tools and treatments that will identify patients at risk for the development of chronic pain, and implement effective management strategies as early as possible. Specialists in pain medicine truly believe that the old adage “An ounce of prevention is worth a pound of cure” applies as much to the disease of pain as any other aspect of medicine.

**INSIDE THIS PUBLICATION**

This publication has been developed to provide MCOs and their P&T committees with an understanding of how effective control of chronic pain can have a positive impact on overall patient care, improve quality of life,

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**FIGURE**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cost per condition (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain</td>
<td>$197.9</td>
</tr>
<tr>
<td>Heart disease</td>
<td>$170.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>$112.3</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>$90.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>$85.6</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>$67.5</td>
</tr>
<tr>
<td>Arthritis</td>
<td>$64.4</td>
</tr>
<tr>
<td>Cancer</td>
<td>$55.0</td>
</tr>
<tr>
<td>Depression</td>
<td>$44.8</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>$42.2</td>
</tr>
<tr>
<td>Stroke</td>
<td>$37.9</td>
</tr>
<tr>
<td>Dementia</td>
<td>$14.8</td>
</tr>
<tr>
<td>Anxiety</td>
<td>$13.6</td>
</tr>
<tr>
<td>HIV infection</td>
<td>$4.9</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>$3.3</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>$2.2</td>
</tr>
</tbody>
</table>

Based on year-1992 claims from adults in a 400,000-member, staff-model HMO. Costs were calculated by multiplying the number of patients by the mean cost per patient. “Chronic pain” includes back & neck pain, facial pain, and headache. Costs shown are applicable only to the Seattle market. Fourteen percent of the population studied had two or more chronic conditions. One limitation of this analysis of the author’s data is that because the presence of a chronic comorbidity contributes to costs for each condition, apples-to-apples comparisons about the costs of specific conditions are difficult to make.

SOURCE: ADAPTED FROM FISHMAN 1997
and reduce utilization of health care resources. It defines pain types, outlines the basic challenges in treating chronic pain — including matching the appropriate medication to the specific category of pain — and reviews accepted practices and guidelines for addressing those challenges. Special concerns, such as chronic pain in the elderly, managing psychological comorbidities, and adopting a multidisciplinary team approach to pain control, are discussed. We are privileged to have several prominent specialists in the field of pain management address these and other significant issues. These areas of concern have emerged as points of significant interest to MCOs in their assessment of pain management strategies to provide the most effective treatments to patients in a timely and cost-effective manner.

**Categories of pain**

Misha-Miroslav Backonja, MD, focuses on definitions of pain. Because the discipline of pain management is still young, the most frequently encountered terms to define major types of pain are inadequate, he argues. Reviews of the pain literature suggest that nociceptive pain generally encompasses pain related to tissue damage caused by mechanical, thermal, or chemical excitation of peripheral nerve fibers. Postoperative pain, caused by direct tissue injury, is a commonly described as nociceptive pain. Neuropathic pain is commonly found in the literature to refer to pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system, spinal cord, or brain.

As Backonja notes, however, this dichotomy can be inaccurate; in trying to describe pain as fitting one of these two categories, one quickly encounters semantic constraint because some types of pain can be either nociceptive or neuropathic. Backonja posits that the best-described types of somatic pain mechanisms that have clinical relevance are inflammatory and neuropathic, and offers examples of both. Aptly, he has dismissed the term psychogenic pain, as all human experiences, including pain, engender a psychological response. Learning to recognize the different types of pain is a critical goal, because only when we correctly categorize pain can we begin to study and implement the most appropriate therapies.

**Prevalence and economic implications of chronic pain**

Hsiupei Chen, MD, provides the most current data on the prevalence of various types of pain, the direct and indirect costs of pain in the managed care setting, and the clinical and financial impact of untreated pain. Estimates of the prevalence of clinically significant pain vary widely, depending on what is being measured and how.
second-line medications for the treatment of neuropathic pain have been rigorously studied in large, randomized, controlled trials. Because neuropathic pain is a unique entity that needs to be treated separately from other pain conditions, Argoff’s article will help clinicians and MCOs understand that the treatment algorithm and medications used to treat neuropathic pain will be substantially different and possibly more complex than those used for typical postoperative or posttraumatic pain.

**Risk management for opiates**

Bill H. McCarberg, MD, offers a thought-provoking discussion on the controversies and concerns surrounding opioid use that have contributed to the well-documented underutilization of these agents. Although risk management for opiates is a serious and significant part of the practice of all clinicians who treat pain, preliminary data suggest that the incidence of addiction is no higher in the pain population than in the community at large (Cowan 2003). McCarberg provides practical definitions of addiction and addictive/aberrant drug-seeking behavior to aid health care professionals in identifying at-risk patients early in the treatment process. He also discusses the movement by national societies to develop risk stratification tools to help screen patients for their drug abuse potential. Although these screens may not be 100 percent effective, they will allow us to identify patients or individuals who may benefit from substance abuse treatment or other management strategies.

This article also sheds light on the serious problem of diversion, which occurs when a patient uses pain medication as a source of income, trading it for another drug or for food. To curtail this illegal activity, physicians must identify at-risk patients and perform definitive blood and/or urine tests to confirm that the patient is taking the medication as prescribed. McCarberg also describes the use of validated tools (e.g., Screening Opioid Assessment for Patients in Pain) that MCOs can use to educate physicians and their patients on the proper use of pain medications.

Another aspect of risk management noted by McCarberg revolves around primary care physicians’ hesitation to use certain pain medications out of fears of prosecution. The federal government recently provided guidance on this subject in a consensus document published in the *Journal of Pain and Palliative Care Pharmacotherapy*, which McCarberg summarizes. In short, the U.S. Drug Enforcement Administration has provided guidelines to clinicians for the use of opioids in chronic nonmalignant pain, and has stated clearly that police and regulatory personnel should not interfere with medical practice and that clinicians have an obligation to practice in a legal manner (DEA 2005).

**Delivery systems**

Joshua Cox, PharmD, RPh, describes the various routes of administration of pain medications. As Cox notes, however, the availability of various routes of administration of analgesics can add to the sometimes perplexing decisions associated with selecting an appropriate, efficacious, and cost-effective regimen to manage chronic pain. Hence, improved understanding of the advantages and disadvantages of each route of administration is beneficial to clinicians and formulary decision makers alike.

As Cox notes, the oral route is the preferred route for analgesic administration. Alternative formulations of pain medications, particularly opioids, allow for alternative routes of administration in the appropriate clinical settings. Patients with altered gastrointestinal motility and poor absorption are candidates for rectal, intravenous, mucosal, and subcutaneous delivery systems. In patients unable to tolerate systemic opioids with an opioid-responsive pain syndrome, neuraxial (epidural or intrathecal) delivery may offer distinct advantages. In patients with focal pain syndromes, such as postherpetic neuralgia, topical delivery of analgesics (such as the local anesthetic lidocaine) offers the benefits of targeted therapy without systemic side effects. As evident by Cox’s article, the technology and pharmacologic options exist to manage pain effectively in virtually any clinical scenario.

**Pain management in the elderly**

Pain management in the elderly is a growing concern for MCOs as the population ages and begins to develop chronic pain conditions. Thus, maintaining functionality and quality of life in the later years will be a primary goal for patients and the health care system.

Perry G. Fine, MD, explores the many challenges of chronic pain management in the elderly. These considerations include the importance of selecting medications that do not decrease independence, do not impair quality of life because of intolerable side effects, and are appropriate for use in considering the pharmacokinetic effects in older patients.

**Multidisciplinary approach**

As with the treatment of complicated diseases, such as breast cancer, the contemporary management of chronic pain is a complex endeavor that requires a true collaborative team approach, characterized by ongoing communication and active information-sharing among the multiple disciplines involved (Rabinowitz 2004). In the final article in this publication, Christopher Edwards,
INTRODUCTION

PhD, a psychologist, examines how a multidisciplinary team that includes physicians, nurses, physical therapists, social workers, and psychologists can work together to create a cost-effective interdisciplinary pain management program that benefits both the patient and the MCO. Edwards provocatively discusses some of the unique challenges confronting the multidisciplinary team, such as handling issues of diversity and reimbursement. As he observes, patients of different ethnicities and religious backgrounds often perceive pain and treatments differently, and it is important for the treatment team to understand how such issues affect a patient’s care or willingness to cooperate with a treatment regimen.

Edwards also examines the concomitant psychological manifestations that accompany chronic pain and how they, too, require the active involvement of multiple health care disciplines. Patients with chronic pain experience activation in parts of the brain associated with increased anger, agitation, irritability, and depression. This is part of the chronic pain process. Unfortunately, the patient and/or the treating physician often may fail to recognize these manifestations. Edwards describes a team approach that employs behavior therapists and other trained mental health specialists to help patients learn coping skills to manage their pain. Unfortunately, many ancillary services required for multidisciplinary management have little or no coverage by many third-party payers. Recognizing the need for multidisciplinary management and providing adequate resources for the implementation of cognitive-behavioral therapies is a very important aspect of reducing the overall biopsychosocial burden of chronic pain.

CONCLUSION

As our understanding of the mechanisms involved in chronic pain improves, so too does the opportunity to manage patients better and improve their quality of life. We hope that the articles in this publication highlight the most significant issues in pain management for managed care decision makers, and that they will provide useful information that ultimately will result in better outcomes for individuals with chronic pain. Early implementation of cost-effective treatment strategies and avoiding unproven or unnecessary treatments can improve clinical outcomes and achieve those outcomes in a cost-efficient manner.

REFERENCES


Pain is of undeniable importance for our survival and well being, but the word pain itself hinders our further understanding of the experience of pain along with our efforts to contain it when it becomes chronic and diminishes quality of life. First, the word is asked to perform multiple roles, being variously applied to a sensory phenomenon, a signaling system, and the condition treated in medical offices when the symptom becomes the disease. Second, because of the often self-imposed limitations of our broader vocabulary for discussing pain in clinical and research settings, pain as a field of research and as an area of clinical focus is severely constrained by a linguistic straitjacket.

In this article, I explain the problems with our terminology and their implications for patient care, and elaborate on my proposal for thinking about pain, especially neuropathic pain, in terms more specific than those we have been using.

LINGUISTIC CONFUSION

A cursory examination of the scholarly literature about pain shows that terms such as nociceptive, neuropathic, and psychogenic pain are frequently encountered. Let us begin by dismissing one of these terms, and relegating another to a more limited role. I suggest that we banish the term psychogenic pain, on the grounds that it is essentially pejorative. People with psychiatric disorders experience pain. Clinicians must approach pain in these patients with appropriate diligence and aim to arrive at a specific diagnosis appropriate to the pain complaint and the underlying pathophysiology. A clinician’s inability to ascertain the source of the pain — a common and understandable failing owing to the complexity of pain — is no justification for suggesting a patient may be mentally unsound. Patients with psychiatric disorders may also have an impaired ability to achieve sustainable coping mechanisms for a painful condition.

As for nociceptive pain, this term is better restricted to the laboratories where it originated. The term is redundant: Nociception is the transmission of pain, and anything that occurs as the result of it is painful, so then the

DEFINITIONS

MISHA-MIROSLAV BACKONJA, MD

University of Wisconsin

SUMMARY

Patients will be best served if researchers and clinicians strive to sharpen the terminology they use to discuss the complex topic of pain. The two types of pain most frequently encountered are inflammatory and neuropathic pain. Improved treatment of pain will occur only through better knowledge of disease processes and pain mechanisms.

1Misha-Miroslav Backonja, MD, is associate professor in the Departments of Neurology, Anesthesiology, and Rehabilitation Medicine at the University of Wisconsin Medical School. He serves as director of the Neuropathic Consultative Pain Service and of research and education for the Pain Treatment and Research Center, and is medical codirector of the Pain Patient Care Team and Acute In-patient Pain Consultation Service at the University of Wisconsin Hospital and Clinics (UWHC). Backonja received his medical degree from the University of Zagreb, Croatia. He completed his residency in neurology and a fellowship in pain management, both at UWHC. An active member of many professional societies, Backonja serves on the Neuropathic Pain Section for the International Association for the Study of Pain and on the Development of Neuropathic Pain Survey Tool task force for the American Pain Foundation. Well published, Backonja has authored or coauthored numerous journal articles, books, book chapters, and abstracts.
DEFINITIONS

term means “painful pain.” It was originally used to describe controlled studies in which a physiological stimulus (e.g., heat or pinprick) was employed to activate the pain-transmitting component of the nervous system. Such controlled pain ceases when the stimulus no longer is applied. This kind of pain is not encountered in clinical settings or even in daily life. Nonetheless, the term is used widely to refer to many kinds of pain, as in this recent example: “Nociceptive pain is a response triggered by an unpleasant damaging or potentially damaging stimulus in the periphery and can be acute in nature, such as acute postoperative pain. It may also be chronic…” (Harden 2005).

Setting aside etymological problems, the types of pain typically described as falling under the heading nociceptive are so varied that the term undermines attempts to classify pain in more specific terms. Advances in the treatment of pain will occur only through improved knowledge of disease processes and pain mechanisms. These advances in our knowledge will necessarily include the elucidation of specific mechanisms that are important during the temporal evolution of the chronic pain state.

At present, the best-described types of somatic pain mechanisms that have clinical relevance are inflammatory and neuropathic. Taking both into consideration, we can construct a spectrum for certain kinds of pain (Table 1), and we also can conceive of them as occupying a continuum that proceeds along two axes — one indicating the severity of inflammatory pain mechanisms and the other the severity of neuropathic pain mechanisms (Figure).

Most certainly, more than two such axes exist, but we do not as yet have the diagnostic tools to describe them in a quantitative manner. Examples of other conditions that are not easily classified in only two dimensions include migraine headaches, visceral pain, cancer-related pain, myofascial pain, and fibromyalgia. These pain states have components of inflammatory and neuropathic pain in addition to other elements that are not well characterized.

The consequences of linguistic confusion and vagueness with respect to the terms we use to describe pain are profound. If our language is inadequate for describing the problems we wish to address, then we will be hindered in learning what we need to know to develop a more sophisticated understanding of chronic pain in general and neuropathic pain in particular. Improved classification and terminology will be important for the future development of more effective therapies. Moreover, if third-party payers perceive that a medical field is floundering in a terminological morass, they are likely to question the wisdom of devoting resources to it.

NEUROPATHIC PAIN

Our ability to identify the pathophysiological mechanisms underlying neuropathic pain is limited, largely because complex numerous peripheral and central nervous system processes are triggered by neural injury (Dworkin 2003, Woolf 2004). At the local level, inflamma-

<table>
<thead>
<tr>
<th>Type of pain</th>
<th>Example</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological pain</td>
<td>Controlled pinprick, heat pulse</td>
<td>Pain ceases with termination of stimulus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No inflammatory component</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Has no clinical application; used in the laboratory to study physiological characteristics and mechanisms of the pain system</td>
</tr>
<tr>
<td>Acute inflammatory pain</td>
<td>Abscess, surgical wound</td>
<td>Pain ceases with wound healing</td>
</tr>
<tr>
<td>Chronic inflammatory pain</td>
<td>Rheumatoid arthritis</td>
<td>Continuing inflammation promotes disease progression</td>
</tr>
<tr>
<td>Neurogenic inflammatory pain</td>
<td>Complex regional pain syndrome, intradermal capsaicin</td>
<td>Severe, often burning, pain persists long after injury should have healed; area often remains swollen</td>
</tr>
<tr>
<td>Inflammatory neuropathic pain</td>
<td>Inflammatory demyelinating polyneuropathy</td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>Central pain, phantom pain, painful diabetic neuropathy, postherpetic neuropathy</td>
<td>See text and Table 2</td>
</tr>
</tbody>
</table>

SOURCE: BACKONJA 2003A
DEFINITIONS

Peripheral sensitization—heightened excitability of the primary nociceptive afferents, nociceptors, and their corresponding peripheral sensory nerves (Bridges 2001, Ji 2004, Kidd 2001). The central neurons innervated by these nociceptors then become hyperexcitable. Under normal circumstances, these states of peripheral and central sensitization resolve upon healing of the peripheral tissue, but they may persist if injury or disease results in ongoing activation of primary afferent neurons.

The definition of neuropathic pain suggested by the International Association for the Study of Pain—“pain initiated or caused by a primary lesion or dysfunction of the nervous system”—is inadequate, chiefly because dysfunction invites use of the term as a catch-all for types of pain that may have a neurological component but have an underlying mechanism other than a neural lesion, or types that are simply difficult to categorize, as so often happens because of the numerous complex biological reactions involved in pain of any kind. It is important for clinicians to resist the temptation to squeeze patients into categorical boxes that do not have specific meanings, such as dysfunction. An additional element of confusion comes from the fact that all pain is conducted by the nervous system. A normally functioning nervous system and biologic response to tissue injury may necessarily include components of peripheral and central sensitization. However, persistent and exaggerated indicators of sensitization would be indicators of neuropathic pain, though it is the clinical evaluation that would document these abnormalities and would prove or disprove the presence of neuropathic pain.

I propose instead that we distinguish between neuropathic pain that can be linked to diagnostically discernable pathoanatomical attributes and neuropathic pain that, for the present, can be described only in terms of pathophysiology. When we achieve a high degree of clinical certainty that a patient has neuropathic pain, then that categorical designation should be applied. If, however, it is not certain what the patient has, then the uncertainty should be stated as such; then we should be able to continue with clinical practice and research, allowing the existence of the category “not certain,” as is the case in most of medicine. The latter category could be labeled hypersensitivity pain disorders, reflecting their common association with allodynia and hyperalgesia (see glossary, page 13).

Although neuropathic pain can be distinguished from inflammatory pain in general terms (Table 2), neuropathic pain confounds clinicians for two reasons. First, a wide range of signs and symptoms are found among patients whose etiology of neuropathic pain is the same. For example, in a prototypical case of postherpetic neuralgia, patients have symptoms that range from complete numbness to allodynia. Second, patients with neuropathic pain of differing etiologies often have signs and symptoms that are similar. That is the case with the conditions plotted in the figure—-the pain-related signs and symptoms associated with each condition are quite similar, despite their divergent etiologies.

The defining characteristic of neuropathic pain from any cause is an injury or a disease of the nervous system. It is likely that the development of neuropathic pain has a genetic predisposition. Clinical observations suggest that pain is not part of the presentation of many neurological disorders that affect the thermoneciceptive components of the nervous system. For example, not every patient with diabetic neuropathy develops painful diabetic neuropathy. This raises the question of whether different, genetically based pathological mechanisms are at play in patients whose diabetic neuropathy becomes painful. If so, identification of the culpable genes and their products might lead to ways to pinpoint diabetic patients with an elevated risk for painful diabetic neuropa.

<table>
<thead>
<tr>
<th>Spectrum of inflammatory and neuropathic pathophysiological mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurogenic pain mechanisms</td>
</tr>
<tr>
<td>Inflammatory pain mechanisms</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>OA</td>
</tr>
<tr>
<td>RA</td>
</tr>
<tr>
<td>PHN</td>
</tr>
<tr>
<td>Phantom pain (post-trauma)</td>
</tr>
</tbody>
</table>

CIDP=chronic inflammatory demyelinating polyneuropathy, CRPS=complex regional pain syndrome, OA=osteoarthritis, PDN=painful diabetic neuropathy, PHN=postherpetic neuropathy, RA=rheumatoid arthritis.

SOURCE: BACKONJA 2005
DEFINITIONS

Neuropathic pain does not occur in isolation, but rather emerges in concert with some disease or injury that affects other tissues and organ systems. For this reason, it is often accompanied by other types of pain, most frequently musculoskeletal. Clinicians must remember to search for and identify these coexisting types of pain in the construction of an appropriate treatment plan.

MULTIDIMENSIONAL APPROACH TO PAIN

Due to the complexities of classification and treatment, a multidimensional approach is needed to assess and treat chronic pain, as with any chronic condition. For example, in addition to careful monitoring and tight control of blood glucose levels, comprehensive care for a patient with diabetes would encompass periodic monitoring of blood pressure, hypertension, and dyslipidemia; screening for coronary disease and instituting antiplatelet therapy for patients with an elevated risk of cardiovascular disease; periodic screening for diabetic retinopathy; periodic screening for nephropathy; annual foot examinations and appropriate foot care; and lifestyle modifications, such as smoking cessation, dietary adjustments, and exercise.

Treatment of chronic pain is no less complex. We suggest that it begin with a formal assessment of pain in four dimensions: medical etiology, pain mechanisms, psychologic comorbidity, and function and quality of life (Table 3). The multidimensional pain assessment should

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Differences between inflammatory pain and neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source of pain</td>
<td>Tissue response to pathological processes that lead to tissue destruction</td>
</tr>
<tr>
<td>Signaling</td>
<td>Activated nociceptor in periphery</td>
</tr>
<tr>
<td>Duration of pain</td>
<td>Ends when healing process is complete</td>
</tr>
<tr>
<td>Peripheral and central sensitization</td>
<td>Ends once tissue heals and inflammation subsides</td>
</tr>
<tr>
<td>Neurological evaluation</td>
<td>Normal, provided disease/injury that caused inflammatory pain did not affect nervous system</td>
</tr>
<tr>
<td>Responds to NSAIDs</td>
<td>Yes</td>
</tr>
<tr>
<td>Responds to anticonvulsants</td>
<td>No</td>
</tr>
</tbody>
</table>

NSAIDs=nonsteroidal anti-inflammatory drugs. SOURCE: BACKONJA 2003A, DWORIN 2003

<table>
<thead>
<tr>
<th>TABLE 3</th>
<th>Multidimensional pain assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimension</td>
<td>Parameters</td>
</tr>
<tr>
<td>I. Medical etiology</td>
<td>Specific medical etiology related to pain; medical comorbidities that could influence manifestation of pain symptoms</td>
</tr>
<tr>
<td>II. Pain mechanisms</td>
<td>Neuropathic, inflammatory, myofascial, etc.</td>
</tr>
<tr>
<td>III. Psychiatric comorbidity</td>
<td>Psychiatric comorbidity; patient’s coping skills</td>
</tr>
<tr>
<td>IV. Function, quality of life</td>
<td>Impact of pain on ability to function, quality of life</td>
</tr>
</tbody>
</table>

Severity rating (none, mild, moderate, severe or 0, 1, 2, 3)

SOURCE: BACKONJA 2005
DEFINITIONS

be used in concert with a traditional validated tool for rating pain intensity and any other assessment tool appropriate for specific elements of the multidimensional pain assessment. For example, neuropathic pain could be specifically assessed by using neuropathic pain questionnaires, such as the Neuropathic Pain Scale (NPS) and the Neuropathic Pain Questionnaire (NPQ) (Galer 1997, Backonja 2003b). The advantage of this approach in the practice setting is that it provides a mechanism for the clinician to contemplate all four dimensions simultaneously and in relation to each other, and as such raises the standard of care for patients with pain, instead of focusing on the single dimension the clinician finds most comfortable or convenient, to the exclusion of others.

A comprehensive treatment plan would follow from this assessment. For example, a patient might present with moderately severe low back pain that originated with degenerative disc disease. Inflammation has compressed the nerve, and hypothyroidism has added to the complexity of the injury, causing neuropathic pain. In addition, the patient has severe depression. The patient is often absent from work, and when at work, his or her performance is adversely affected. Each factor requires separate treatment, which is best provided by an intensive, multidisciplinary program that simultaneously addresses medical, psychological, and rehabilitative components (Carragee 2005). The approach to this patient will be dramatically different from that for another patient with a similar-looking disk, but with severe pain and comorbidity of uncontrolled hypertension and associated renal dysfunction and no depression.

Treatment planning has to take into account not only the mechanisms of pain and the natural course of the disease, but also each patient's goals. Certainly, treatment planning should be framed within the limits of available therapies and resources.

Glossary of terms and acronyms

Algogenic. Pain-inducing.
Allodynia. Painful response to a nonnoxious stimulus, such as the light touch of a finger or feather.
Analgesia. Absence of pain in response to normally painful stimulus.
Central sensitization. Long-lasting changes in spinal excitability stemming from sustained or repetitive activation of primary afferent neurons (see peripheral sensitization).
CRSP. Complex regional pain syndrome.
Deafferentation. Temporary or permanent loss of primary afferent fibers owing to injury or disease.
Dysesthesia. Unpleasant, abnormal sensations, either evoked or spontaneous, that may be experienced by patients with neuropathic pain; distinct from pain in the classical sense.
Hyperalgesia. Heightened response to a normally painful stimulus.
Hyperesthesia. Increased sensitivity to stimulation.
Hyperpathia. Syndrome characterized by abnormally painful reaction to a stimulus, especially repetitive stimulus.
Hypersensitivity pain disorders. Suggested category (possibly transient) for chronic pain disorders with signs and symptoms that are suggestive of neuropathic pain mechanisms but, owing to limits of currently available diagnostic tools, do not rise to the level of clinical specificity needed to define neuropathic pain.
Hypoalgesia. Diminished pain in response to normally painful stimulus.
Hypoesthesia. Decreased sensitivity to stimulation.
IPN. Inflammatory pain; pain resulting from tissue response to disease or injury, i.e., pathologic processes involved in tissue destruction (e.g., abscess, fresh wound). Responds readily to NSAIDs.
Neuropathic pain. Suggested category for pain arising from disease or injury of the thermonociceptive component of the nervous system, at any level (i.e., peripheral, central, or both).
Nociceptive. Painful; involving the pain-transmitting components of the nervous system.
Nociceptive pain. Commonly used but unhelpful term (redundant, means "painful pain"), being an artifact of laboratory studies that have no application to clinical practice; better replaced by physiological pain.
Paresthesia. Abnormal sensation, either evoked or spontaneous, that may be experienced by patients with neuropathic pain.
PDN. Painful diabetic neuropathy.
Peripheral sensitization. Modification (by inflammatory mediators) of the response properties of primary afferent neurons, creating a state of hyperexcitability.
PHN. Postherpetic neuralgia.
Physiological pain. Pain arising from a stimulus (pinprick, heat pulse) that activates the temperature- and pain-transmitting (thermonociceptive) nervous system.
Psychogenic pain. Pejorative term related to unclassified pain experienced by psychiatric patients; not helpful.
Thermonociceptive. Relating to the temperature- and pain-sensing components of the nervous system.
CONCLUSION

Over the long term, patients with pain will be best served if researchers and clinicians strive to sharpen the terminology they use to discuss the complex topic of pain. We recommend dropping *psychogenic pain* and *nociceptive pain* from common usage, owing to their lack of precision, and, in the case of the former, its propensity to inflict psychological harm. We also suggest reserving *neuropathic pain* to describe pain that is the result of injury or disease of the nervous system, and adopting *hypersensitivity pain disorders* for conditions with components of neuropathic pain but which, for the moment, can be described only in pathophysiological terms.

With improved communication, along with new methods, tools, and therapeutic advances now available to clinicians, patients today can receive comprehensive and specific treatments for their chronic pain.

REFERENCES


When pain becomes a constant companion, it diminishes the quality of life, increases the use of health care resources, and carries numerous implications for the economy and productivity. Chronic pain — persistent pain lasting for more than 3 months — rarely resolves spontaneously and prompts between 10 and 20 percent of primary care visits (Marcus 2005).

Hsiupei Chen, MD, is an anesthesiologist and pain management specialist at Carolina Pain Consultants, in Raleigh, North Carolina. Chen completed her bachelor of arts degree at Princeton University and earned her medical degree at Duke University School of Medicine. Her postgraduate studies include a residency in anesthesiology at University of California—San Francisco and a clinical fellowship in chronic pain management at the Duke Pain and Palliative Care Clinic, in Durham, North Carolina. Chen, who has published reviews of pharmacologic management of neuropathic pain and management of neuropathic pain in primary care, has given presentations on pharmacogenetics and other aspects of pain management across the United States and in Taiwan.
(46.1 percent). At the end of the measurement year, 49.1 percent of patients overall had not recovered from persistent pain (range, 16.7 percent [Athens] to 79.4 percent [Ankara, Turkey]); in Seattle, the rate was 54.9 percent. The presence of two or more pain sites at baseline was the strongest clinical predictor of nonrecovery.

In this study, a symmetrical relationship was observed between persistent pain and psychological disorders (anxiety or depressive disorders). That is, the presence of persistent pain at baseline predicted the onset of a psychological disorder among those free of such disorders at baseline. Likewise, the presence of a psychological disorder at baseline predicted the onset of persistent pain. Patients with persistent pain were much more likely to have a depressive or anxiety disorder than patients without pain (overall, 33.7 percent vs. 10.1 percent; U.S., 18.5 vs. 5.5 percent).

In a managed care population, back and neck pain was the chronic condition with the highest treated prevalence, significantly higher than heart disease and hypertension (Fishman 1997). Arthritis and headache ranked sixth and eighth in treated prevalence (Figure 1). Moreover, the age-adjusted mean costs associated with specific painful conditions were comparable to those for treating other chronic conditions, and total annual costs for all chronic pain were higher than any other chronic condition (see article by Brewer: Figure, page 5).

**Geriatric population**

In four studies that have directly measured the prevalence of pain among residents of U.S. nursing homes and other institutions through self-reporting or chart review, the prevalence of pain has ranged from 62 percent to 80 percent (Fox 1999). Musculoskeletal conditions were the predominant painful condition. It also has been reported that between 45 percent and 80 percent of nursing home residents are beset by pain that impairs function (Davis 2003). In addition to musculoskeletal conditions, pain in this population is caused by peripheral vascular disease, peripheral neuropathies, stroke, shingles, diabetes, and trigeminal neuralgia.

Nationwide, 3.7 percent of nursing home residents experience daily pain that was “excruciating” at one or more times during the previous week (Teno 2004). The prevalence of excruciating daily pain varied widely from state to state, ranging from 1.9 percent in New York to 6.8 percent in California. Compared with patients without excruciating pain (n=2,054,487), those with excruciating pain (n=80,512) were more likely to have been hospitalized in the previous 90 days (68.3 percent vs. 41.4 percent) and more likely to have cancer (20.9 percent vs. 8.6 percent). The conditions most likely to be associated with excruciating pain were cancer, pressure ulcer, and hip fracture. Excruciating pain was less likely to be reported among black patients compared with white patients, in patients with cognitive impairment compared with patients who were cognitively intact, and in patients 65 and older compared with those younger than 65. The reported rates of excruciating pain declined steeply with increasing age.

Another recent study employed a cross section of the Minimum Data Set (Won 2004). Persistent pain was defined as the presence of any pain recorded in at least 2 of 3 quarterly assessments that were performed over a span of 6 months. The study was restricted to patients from the 10 states that had complete pain and drug data for five quarterly assessments. Data were analyzed for residents ages 65 and older without a diagnosis of cancer or a terminal condition, and whose cognitive and communicative abilities were not moderately or severely impaired. In this population, the prevalence of persistent pain was 48.5 percent; it was highest among patients with musculoskeletal pain (66.3 percent), a history of surgery (63.6 percent), and a fracture in the past 6 months (62.9 percent).
COMMON CHRONIC PAIN CONDITIONS
Musculoskeletal conditions

Musculoskeletal disease is the most common cause of nonmalignant chronic pain (Katz 2002). Back problems and arthritis together accounted for nearly 10 percent of the increase in private insurance spending between 1987 and 2002 (Thorpe 2005). An increase in treated prevalence, rather than an increase in cost per case, was the primary driver of increased expenditures; a 60 percent increase in the treated prevalence of arthritis accounted for 60 percent of its contributions to the total growth in spending.

The prevalence of arthritis and other rheumatic conditions rises steeply with age. It is found in 21 percent (42.7 million) of U.S. adults overall in the civilian noninstitutionalized population, 8 percent of whom are between the ages of 18 and 44; 29 percent are age 45 to 64; and 48 percent are 65 or older (CDC 2005). Among adults with physician-diagnosed arthritis, 25 percent (10.5 million) reported severe joint pain during the prior 30 days. More than one third reported activity limitations, and among those ages 18 to 64, 30 percent reported work limitations attributable to arthritis.

Already the leading cause of disability among U.S. adults, the prevalence of arthritis and other rheumatic conditions is predicted to rise dramatically in the noninstitutionalized elderly as the U.S. population ages (Figure 2). If the prevalence rates of arthritis and related disorders remain stable between now and 2030, the number of Americans with these conditions will nearly double.

People with arthritis and other rheumatic conditions incur medical expenditures disproportionate to their numbers. Data from a nationwide sample of households, the Medical Expenditure Panel Survey (MEPS), showed that among noninstitutionalized adults in 1997, about 38.4 million (14.2 percent of the U.S. population) reported arthritis and other rheumatic conditions, for which direct medical costs amounted to $51 billion (Yelin 2004). Of this group, however, 85 percent reported at least one additional condition. Their total medical expenditures amounted to $187 billion, or 34 percent of medical care expenditures. Total lost wages for patients with arthritis and other rheumatic conditions amounted to $82 billion, with $35 billion being attributable to these conditions. Altogether, these patients incurred $269 billion in direct and indirect costs — more than 2 percent of GDP — of which $85 billion was directly attributable to arthritis and other rheumatic conditions.

Osteoarthritis. The most frequently encountered form of arthritis is osteoarthritis — the most common reason for costly total hip and total knee replacements and a major contributor to the broader problem of musculoskeletal pain and disability (Felson 2000). Sometimes osteoarthritis arises from severe joint injury, but more often, it stems from the interaction of systemic factors (age, sex, bone density, genetics) and local biomechanical factors (obesity, joint injury, joint deformity, muscle weakness, participation in competitive sports, and occupational activities such as repetitive motion, kneeling, and squatting).

Some patients with clinical signs of osteoarthritis remain asymptomatic. One of the lines of evidence suggesting that osteoarthritis may be several distinct entities with a common final pathway, instead of a single disease, is the existence of distinct forms of osteoarthritis of the hip — hypertrophic and atrophic. This finding has im-

<table>
<thead>
<tr>
<th></th>
<th>Overall (N=12,856)</th>
<th>Men (n=5,089)</th>
<th>Women (n=7,767)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequent headache (≥180 per year)</td>
<td>4.1 (%)</td>
<td>2.8 (%)</td>
<td>5.0 (%)</td>
</tr>
<tr>
<td>Chronic tension-type headache</td>
<td>2.2 (%)</td>
<td>1.6 (%)</td>
<td>2.6 (%)</td>
</tr>
<tr>
<td>Migrainous features</td>
<td>1.3 (%)</td>
<td>0.7 (%)</td>
<td>1.7 (%)</td>
</tr>
<tr>
<td>Unclassified</td>
<td>0.7 (%)</td>
<td>0.5 (%)</td>
<td>0.8 (%)</td>
</tr>
<tr>
<td>Episodic tension-type (&lt;15 per month)</td>
<td>38.3 (%)</td>
<td>36.3 (%)</td>
<td>42.0 (%)</td>
</tr>
</tbody>
</table>

applications for mechanistic drug-based strategies aimed at preventing and treating osteoarthritis.

In a managed care population, although the prevalence of osteoarthritis increased with age, the majority of the patients with clinically significant osteoarthritis during a 12-month period were younger than 65 (Mapel 2004). Compared with matched controls, patients with osteoporosis were 4 times more likely to be hospitalized and made more than twice as many outpatient visits as the controls. The direct medical costs of caring for patients with osteoarthritis were as high as or higher than those for patients with other chronic medical conditions, with much of the excess utilization devoted to services not usually associated with musculoskeletal disease.

Headache

A telephone survey of the general population in Baltimore County, Md. (a demographically diverse region), found that the annual prevalence of episodic tension-type headache is 38 percent (Schwartz 1998). The prevalence of frequent headache (180 or more headaches per year) in the overall population is 4.1 percent (Scher 1998). Episodic tension-type headaches and frequent headaches were more common in women than men (Table 1, page 17).

Migraine. Migraine is a particularly debilitating disorder that affects at least 10 percent of the U.S. adult pop-
Neuropathic pain

About 4 million people in the United States suffer from various forms of neuropathic pain, as a result of injury to the peripheral or the central nervous system, or both, manifesting with positive and negative sensory phenomena (Backonja 2003). Among the more common of the peripheral neuropathic pain syndromes are diabetic peripheral neuropathy, postherpetic neuralgia, central post-stroke pain, and spinal cord injury.

Analysis of a health claims database for 3 million managed care members (Figure 4) found that within 1 calendar year, about 2 percent (N=55,686; mean age, 58; female, 58 percent) had two or more medical encounters for a painful neuropathic disorder. The most common of these disorders were back and neck pain with neuropathic involvement (62 percent), causalgia (12 percent), and diabetic neuropathy (11 percent). In this population, chronic comorbidities were common: low back pain, 44 percent; other spinal pain, 55 percent; diabetes, 22 percent; osteoarthritis, 14 percent; other arthritis and musculoskeletal pain, 47 percent. Seventy percent of patients with painful neuropathic disorders had more than one comorbidity, compared with 13 percent of age- and gender-matched controls. Compared with the matched controls, patients with neuropathic pain incurred annual health care charges that were 3 times as high.

Painful diabetic neuropathy

Painful diabetic neuropathy is found in about 20 to 24 percent of patients with diabetes mellitus; it is more prevalent among patients with type 2 diabetes, which accounts for 90 to 95 percent of all cases of diabetes (Schmader 2002). As of 2002, it was estimated that 18.2 million Americans (6.3 percent) have diabetes, including 5.2 million in whom it is undiagnosed and hence is untreated (NIDDK 2004). The prevalence of painful diabetic neuropathy in the United States, therefore, can be estimated at about 3.5 million.

The prevalence of diagnosed diabetes in the United States has increased rapidly, from 4.9 percent in 1990 to 6.9 percent in 1999, and the lifetime risk of developing diabetes for Americans born in 2000 is estimated at 33 percent for males and 38 percent for females (Narayan 2003). It is predicted that the prevalence of diagnosed diabetes will increase by 165 percent between 2000 and 2050, with concomitant increases in the prevalence of painful diabetic neuropathy.

Peripheral neuropathy appears to be underdiagnosed among elderly patients, and it commonly is associated with pain and discomfort. In an elderly primary care population (N=795), 31 percent of the patients were found to have peripheral neuropathy, but only 2 percent had a prior diagnosis of peripheral neuropathy. Pain or discomfort (among other symptoms) was reported by 48 percent of the patients in which a neurologic deficit was found. Patients with a disease known to cause peripheral neuropathy (e.g., diabetes) were almost twice as likely to have peripheral neuropathy as patients without a predisposing disease (45 percent vs. 26 percent). Only among patients without predisposing disease did the prevalence of peripheral neuropathy rise with age (Figure 5), but 46 percent of patients ages 85 and older had no neurological deficit. This finding suggests that peripheral neuropathy is not an inevitable consequence of aging, but aging may contribute to its development in the presence of other unidentified factors.

Postherpetic neuralgia

Postherpetic neuralgia is a complication of herpes zoster (shingles), which in turn is caused by reactivation of the varicella zoster virus, the cause of chicken pox. In the United States the annual incidence of herpes zoster is between 600,000 and 800,000 cases, the incidence of which rises sharply with increasing age and immunosuppression (Schmader 2002). The incidence of postherpetic neuralgia also increases with age. Depending on how the prevalence of postherpetic neuralgia is defined, in terms of months after herpes zoster onset, it is found in 8 to 24 percent of herpes zoster patients of all ages but in substantially more patients over age 50.

Central post-stroke pain

Central post-stroke pain emerges in about 8 percent of stroke survivors, usually within the first month after the stroke, but sometimes not becoming manifest until 6 months or more post-stroke (Backonja 2003). Most of these patients experience allodynia, dysesthesia, and hyperalgesia. About 40 percent have hypoalgesia, and about 5 percent experience mod-
erate to severe pain. Because of the delayed emergence of central post-stroke pain, it may be underdiagnosed, although treatment options are limited even when it is recognized. With an estimated 2.5 million stroke survivors in the United States, the number of Americans with central post-stroke pain probably numbers around 200,000.

**Epidemiology**

**Economic Implications of Chronic Pain**

**Back pain**

Only upper respiratory visits rank ahead of low back pain among the symptom-related reasons for which patients visit physicians. Back problems accounted for 3.4 percent of the total increase in private insurance spending between 1987 and 2002, with an increase in treated prevalence of back pain accounting for 138 percent of its increase in spending (Thorpe 2005). In office practice, about 70 percent of the cases of low back pain are attributed to lumbar strain or sprain, but a precise patho-anatomical diagnosis cannot be provided for about 85 percent of patients (Deyo 2001).

Among workers, the prevalence of back pain lasting 1 week or more during a 1-year period was 17.6 percent (22.4 million cases), resulting in 149 million workdays lost in 1988 (Guo 1995). Sixty-five percent of the cases were attributed to occupational activities but, not surprisingly, the risk of work-related back pain was higher in some occupations than in others. In male workers, back pain was most prevalent among construction laborers, carpenters, and operators of industrial trucks and tractors (22.6, 22.2, and 21.8 percent, respectively, compared with 10.7 percent prevalence among all male workers). Among female workers, the occupations with the highest risk for back pain were nursing aides, orderlies, and attendants; licensed practical nurses; and maids (18.8, 16.3, and 14.9 percent, respectively, compared with 6.7 percent prevalence among all female workers).

A study using MEPS data from 1998 found that patients with back pain incurred $91 billion in total health care expenditures (Table 2), and their medical expenditures were about 60 percent higher than those for patients without back pain. Incremental expenditures attributable to back pain amounted to $26 billion. As is true among patients with chronic conditions, a small proportion of high-cost patients accounts for the majority of expenditures: The 10 percent highest-cost patients accounted for 99 percent of inpatient expenditures, 90 percent of emergency visit expenditures, and 87 percent of outpatient expenditures.

In a managed care population, patients with chronic back pain were 3 times more likely than matched controls to be admitted to a hospital, and they also were more likely to use outpatient services (Mapel 2004). Compared with patients in the same population with osteoarthritis (discussed previously), the patients with chronic back pain incurred higher radiology costs and were more likely to visit the pain clinic (31 percent vs. 9 percent). Compared with the control group, patients with chronic back pain incurred prescription drug costs that were more than twice as much ($1,331 vs. $643), with antidepressant utilization being notably higher.

**Lost work productivity**

A nationwide survey of working adults ages 18 to 65 (N=28,902) found that in a 2-week period, common pain conditions (headache, arthritis, back pain, unspeci-

**Table 2**

<table>
<thead>
<tr>
<th>Health care expenditures for back pain, 1998</th>
</tr>
</thead>
<tbody>
<tr>
<td>In billions</td>
</tr>
<tr>
<td>Inpatient care</td>
</tr>
<tr>
<td>Office-based visits</td>
</tr>
<tr>
<td>Prescription drugs</td>
</tr>
<tr>
<td>Outpatient services</td>
</tr>
<tr>
<td>Emergency room visits</td>
</tr>
<tr>
<td>Home health/other</td>
</tr>
<tr>
<td>Total</td>
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</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Predictors of musculoskeletal pain and disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Increasing age</td>
</tr>
<tr>
<td>• Osteoarthritis</td>
</tr>
<tr>
<td>• Obesity</td>
</tr>
<tr>
<td>• Physical inactivity</td>
</tr>
<tr>
<td>• Low personal self-esteem</td>
</tr>
<tr>
<td>• Comorbid conditions from tobacco and alcohol use</td>
</tr>
<tr>
<td>• Depression</td>
</tr>
<tr>
<td>• Low educational level</td>
</tr>
<tr>
<td>• Low socioeconomic status</td>
</tr>
</tbody>
</table>

**Source:** Felson 2000
fied musculoskeletal pain) were reported by 52.7 percent of workers and resulted in lost productive time among 12.7 percent of workers (Stewart 2003a). Lost productive time included absenteeism as well as reduced productivity while at work (presenteeism). In this study, four times as much lost productive time was attributed to pain-related presenteeism as to pain-related absenteeism.

In 7.2 percent of the workers, the common pain conditions resulted in the loss of 2 or more hours of productive time per week, with headache being the most frequently mentioned source of productive time lost (Figure 6). Numerous risk factors contribute to musculoskeletal pain and disability, many of them modifiable through lifestyle changes (Table 3). Obesity in particular has contributed to the increase in the treated prevalence of back problems and arthritis since 1987 (Thorpe 2005).

Over the course of 1 year, the value of the lost productive time owing to these common pain conditions was estimated at $61 billion in 2002 U.S. dollars, 77 percent of which was attributed to reduced performance while at work. Additional data collected during the same survey showed that the total cost of all health-related lost productive time was about $226 billion (Stewart 2003b), so these pain-related productivity losses accounted for 27 percent of that amount.

A retrospective analysis of absentee and claims data for workers with chronic pain who were employed by six large U.S. corporations found that pain-related medical and pharmacy costs amounted to $4,607 per employee per year in 1998 U.S. dollars (Pizzi 2005). Subjects were defined as having chronic pain if they possessed a 3-month supply of a short- or long-acting opioid during the 3-year study period. In this population, the majority of pain-related outpatient visits and hospital admissions were due to musculoskeletal conditions (64.0 and 44.1 percent, respectively). Work loss, usually in the form of short-term disability, was experienced by 61.5 percent of the employees with chronic pain. Excluding worker’s compensation and long-term disability, each employee with chronic pain lost wages averaging $5,339 per year.

**Comorbid depression**

Compared with patients with pain only, patients with depression and pain are more likely to complain of pain and also more likely to experience persistent pain. In a cross-national European telephone survey (N=18,980), major depressive disorder was found in 4.0 percent of subjects, of whom 43 percent had at least one painful physical condition that was chronic (6 months or more) (Ohayon 2003). Compared with patients without a major depressive disorder, patients with a major depressive...
order were 4 times more likely to have a chronic painful physical condition. In particular, they were 5 times more likely to have back pain and four times more likely to have headaches.

In a U.S. managed care population (N=229,776), an analysis of claims data revealed that patients with depression and chronic comorbidities incurred annual medical costs that were 2 to 4 times higher per comorbidity than the costs for patients without depression. With respect to painful conditions, the average annual costs for patients with depression and back pain were 3 times higher, and with depression and migraine, 4 times higher (Figure 7, page 21).

Medication use

In a small percentage of patients, the use of non-steroidal anti-inflammatory drugs to treat chronic pain is associated with serious adverse gastrointestinal events necessitating hospitalization and sometimes resulting in death. An estimated 100,000 such hospitalizations occur annually, with annual direct costs of $2 billion (Wolfe 1999). In addition, adverse events associated with opioids, such as sedation, cognitive impairment, respiratory depression, nausea and vomiting, and constipation, also have economic implications whenever these agents are considered for the treatment of chronic pain. Each of these side effects can, in turn, accrue more costs as additional medications, treatments, or hospitalizations are required.

Note that the direct medical expenses reported in 1997 for arthritis and other rheumatic conditions (Yelin 2004) would not have included any biologic response modifiers or COX-2 inhibitors among the prescription drugs. Although the popularity of COX-2 inhibitors to treat arthritic pain (or pain in general) has declined recently, utilization of biologic response modifiers (BRMs) to treat rheumatoid arthritis is growing and can be expected to increase, especially in light of the National Committee for Quality Assurance’s addition of a BRM-utilization measure to the 2006 Health Plan Employer Data and Information Set. Higher utilization of BRMs could have a significant impact on direct costs of care.

CONCLUSION

In many cases, if not most, persistent pain is avoidable, primarily through measures to prevent the conditions that lead to the pain rather than through the application of therapies to treat pain directly once it has emerged. Of course, in patients already trying to cope with persistent pain, there is no choice but to treat the pain while trying to address its underlying cause. From long-term societal and health plan perspectives, however, preventing the emergence of such conditions as obesity or diabetes through relatively inexpensive lifestyle modifications would reduce the prevalence of back pain, painful osteoarthritis, and painful diabetic neuropathy, and thereby lead to substantial reductions in direct and indirect costs, and also to improved quality of life.

REFERENCES


Guidelines for Pain Management

CHARLES E. ARGOFF, MD
New York University School of Medicine

SUMMARY

Undertreatment of acute and chronic pain still occurs, despite recent advances in assessment and treatment modalities and a steady rise in resources dedicated to pain management. Guidelines for pain management have gained particular importance as they attempt to identify an optimal set of practices. This article reviews recently developed guidelines for management of neuropathic and cancer pain and pain in the elderly, and their implications for MCOs.

Guidelines for pain management attempt to identify an optimal set of practices to provide patients with high quality care (Schmidt 1996, Berry 2000). Medical guidelines are developed by teams of key opinion leaders to: 1) identify practice questions of interest, options, and outcomes; 2) identify and review evidence on prevention, diagnosis, prognosis, therapy, drawbacks, patient needs, and cost-effectiveness; and 3) identify decision points at which the guideline information should be joined with clinical experience (UCSF 2001). Generally, both clinicians and managed care decision makers should frame their review of guidelines with three questions in mind: Are they valid? Are they useful? Are they applicable?

Practice guidelines commonly are developed from the work of a consensus panel of experts and evidence-based guidelines, in which an author panel reviews the medical literature as part of the published guideline, to provide an indication of the relative assessed strength of all available evidence (Woolf 1992, UCSF 2001). The University of California–San Francisco has identified five steps in evidence-based medicine (Table 1).

The best method of developing guidelines is a subject of great debate. In 1992, evidence-based medicine was hailed as the new paradigm (Evidence-Based Medicine Working Group 1992); increasingly, attempts have been made to harness the explosive growth of readily available medical literature to affect clinical decisions. Recently, the consensus panel method of guideline development has come under scrutiny. One study noted that though an assemblage of expert opinion has strength, a guideline devised from a consensus panel can be inadequate, as experts are not always correct (Persons 1998). Consensus methodology also teaches reliance on expert opinion rather than empirical methods, and distinc-
tions between issues for which data do and do not exist can be hazy.

Evidence-based guidelines are intended to forge clear links both between scientific studies and guideline recommendations (Grimshaw 1995) and physician experience and scientific evidence (UCSF 2001). For more than a decade, an increasing number of consensus groups and guidelines have attempted to use the evidence-based approach, combined with ongoing assessment of clinical outcomes to improve patient care via the teaching and implementation of “tools, not rules” (Carr 2001).

GUIDELINES FOR INSTITUTIONS

The field of pain management received support from the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), which since 2001 has required pain assessment and management standards as part of the accreditation process (Table 2). The required institutionalization of standards — across health care networks, hospitals, long-term care facilities, and outpatient clinics — will hopefully increase the incorporation of pain management into daily medical practice.

The American Pain Society (APS) is a multidisciplinary organization dedicated to the advancement of pain-related research, education, treatment, and professional practice. The APS has published a host of guidelines to assist with assessment and treatment of patients suffering from several types of pain. The APS recognizes pain as the “fifth vital sign,” as methods of pain assessment and treatment must now be integrated into overall patient management (Goodman 2003). In 1999, the Department of Veterans Affairs (VA) adopted several APS guidelines when launching a groundbreaking nationwide pain management program targeting 3.4 million people using VA health care services. Part of this program calls for adding pain as the fifth vital sign, with patients being asked to rate their pain on a scale of 0–10. This initial assessment of patient pain is then used as part of the pain management protocol offering access to pain management specialists and multidisciplinary clinics. The VA also systematically monitors patient outcomes and quality of patient outcomes by performing quarterly data collections and analyzing those data across sites (VA 2001). The VA also reaches out to medical students and other health care professionals to provide education on the importance of pain management protocols.

The JCAHO requirements, hopefully, will foster physician acceptance of pain management and help to eliminate barriers to adoption of pain management guidelines. The VA model, meanwhile, will be useful for other institutions. Integrating pain management guidelines into institutional practice improves patient outcomes and satisfaction with respect to their pain management (Carr 2001).

GUIDELINES FOR CLINICAL PRACTICE

Pain classification historically has divided diverse pain states into two major categories, nociceptive and neuro-

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**TABLE 1**

The five steps of evidence-based medicine

1. Convert clinical information needs into answerable questions
2. Track down the best evidence with which to answer them
3. Critically appraise that evidence for its validity (closeness to the truth) and usefulness (clinical applicability)
4. Apply the results of this appraisal in clinical practice
5. Evaluate your clinical performance

**SOURCE:** UCSF 2001

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**TABLE 2**

JCAHO pain standards

All organizations are required to:

- Recognize the rights of patients to appropriate pain assessment and management.
- Identify patients with pain in an initial screening assessment.
- Perform a more comprehensive pain assessment when pain is identified.
- Record assessment results in a way that facilitates regular reassessment and follow-up.
- Educate health care providers in pain assessment and management.
- Determine and assure staff competency in pain assessment and management.
- Address pain assessment and management in the orientation of all new staff.
- Establish policies and procedures that support appropriate prescription or ordering of effective pain medications.
- Ensure that pain does not interfere with participation in rehabilitation.
- Educate patients and their families about the importance of effective pain management.
- Address patient needs for symptom management in the discharge planning process.
- Collect data to monitor the appropriateness and effectiveness of pain management.

**SOURCE:** BERRY 2000
pathic. Nociceptive pain describes pain that may occur as the result of the normal activation of nociceptors. These specialized nerve endings may, with sufficient stimulation, be activated by mechanical, thermal, or chemical stimuli. Clinical examples of acute nociceptive pain include pain associated with injuries, musculoskeletal pain, postoperative pain, and pain associated with childbirth. As suggested by Backonja elsewhere in this publication [pages 9–14], however, this term is believed by many in the field of pain management to be inadequate, and it may soon be supplanted by more descriptive terms, including inflammatory pain. Neuropathic pain describes pain associated with injury or dysfunction in the peripheral and/or central nervous system (peripheral nerve, spinal cord, or brain). Common neuropathic pain syndromes include acute or postherpetic neuralgia, diabetic neuropathy, HIV–associated polyneuropathy, and nerve root injury (radiculopathy). Causal factors for neuropathic pain include infection, trauma, surgery, chemotherapy, and radiation (Dworkin 2003). In general, existing protocols for nociceptive pain tend to have been developed based on the disease state, with cancer pain treatments, for example, receiving wide dissemination.

Guidelines for neuropathic pain

Despite the existence of overall guideline recommendations for neuropathic pain, its heterogeneity — disease states include diabetic neuropathy, trigeminal neuralgia, postherpetic neuralgia, spinal cord injury, HIV, sensory neuropathy, poststroke syndromes and multiple sclerosis — has made treatment challenging (Dworkin 2003, Harden 2003, Chong 2003).

Neuropathic pain symptoms are sometimes believed to be more severe than those of nociceptive pain, but relative severity has not been studied (Grond 1999). Pain relief is suboptimal in a high percentage of patients (Harden 2003), which may be a result of inadequate diagnosis and treatment resulting from a lack of understanding of the underlying etiology of neuropathic pain, confounding or compounding comorbid conditions, lack of education about treatment options, and utilization of suboptimal outcomes measures (Harden 2003). In general, treatment of symptoms is empirical, focuses on restoring function, and is achieved by combining pharmacological interventions as well as maximizing nonpharmacological interventions (Chong 2003).

The 2003 evidence-based treatment recommendations for neuropathic pain were formulated by members of the Faculty of the Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain (Dworkin 2003) from a review of randomized controlled trial evidence and collective clinical experience.

The guidelines recommend the assessment of patient pain to arrive at an adequate diagnosis and to serve as a baseline from which short- and long-term treatment efficacy can be monitored. Assessment tools generally use a numbered continuum scale on which patients rate their symptoms from “no pain” to “worst possible pain.” A review of data from several pain studies revealed that a 30 percent drop on an 11-point pain intensity scale (with 0 being “no pain” and 10 “worst possible pain”) correlates well with a patient’s rating of “moderate relief” or “much improved” pain (Dworkin 2003).

Clearly, patient–reported pain measurements are subjective and may be interpreted differently by clinicians. One report argued for data-driven cutoff points to help clarify the meaning of differences in patient-reported scores in the literature (Farrar 2000). To further explore the validity of data-driven cutoff points, Farrar (2003) reviewed the data from a randomized, double-blind, double dummy-controlled trial (Coluzzi 2001) of a novel cancer pain agent — oral transmucosal fentanyl citrate (OTFC) versus morphine sulfate immediate release. Patients were monitored and asked to self-report pain intensity every 15 minutes for 1 hour; global medication performance was recorded at the end of each pain episode. Data were analyzed from 134 OTFC-naïve patients for 1,307 pain episodes. Utilizing balanced specificity and sensitivity, the best cutoff points were 33 percent for the percent pain intensity difference; > 2 for the raw pain intensity difference on a scale of 0–10; > 2 for pain relief; > 33 percent for the percent maximum total pain relief; and > 2 for global medication performance. These data support earlier findings that cutoff points based on patients’ self-reported severity provide a good surrogate measure of clinical response (Farrar 2003).

The treatment recommendations are, however, derived from an evidence-based approach and consider clinical efficacy, safety, adverse events, quality of life, and associated costs. The maximum length of the trials reviewed was 2 months, however; therefore, the guidelines do not consider long-term safety and efficacy of treatment regimens longer than 2 months (Dworkin 2003). The first-line medications for initial treatment of neuropathic pain are gabapentin, 5 percent lidocaine patch, opioid analgesics, tramadol hydrochloride, and tricyclic antidepressants (Table 3).

When the patient response to the first-line agents is suboptimal, clinicians may consider the second-line treatment options, which include anticonvulsants other than gabapentin (e.g., lamotrigine or carbamazepine) or antidepressants other than tricyclics (e.g. paroxetine, citalopram, venlafaxine, bupropion). If pain persists or increases, capsaicin, clonidine, dextromethorphan, and mexiletine may be effective in individual circumstances and are defined as “beyond the second line” (Dworkin 2003).
In the event of partial response, combination treatment should be considered.

Since the issuance of the Fourth International Conference's guidelines in 2003, the U.S. Food and Drug Administration has approved duloxetine for diabetic peripheral neuropathic pain and pregabalin for neuropathic pain associated with diabetic neuropathy and postherpetic neuralgia.

### Guidelines for cancer pain

The most recent guidelines for cancer pain were published early in 2005 by the APS (Miaskowski 2005). The APS guidelines clearly define the evidence-based procedures used and provide a hierarchy of evidence by type and by strength. Multiple interventions — assessment of cancer pain, management of cancer pain, and management of procedure-related pain in children and adults — were assessed. The guidelines include multiple algorithms — for assessment of cancer pain, for initial treatment of cancer pain, for rapid titration with short-acting oral or intravenous opioids, for slow titration with short-acting oral opioids, and for ongoing treatment of pain in patients with cancer. Table 4, on page 28, lists a summary of major recommendations.

Clinicians are urged to assess patients comprehensively, with attention to the appropriate diagnostic method and measurement instruments. Pain management should focus on involving both patient and caregivers. Additionally, the APS guidelines are similar to those from the Agency for Health Care Policy and Research on acute and cancer pain that stress pain prevention (Schmidt 1996), in that appropriate algorithms emphasize identifying pain-causing mechanisms before symptoms emerge.

### Guidelines for pain in the elderly

The prevalence of chronic pain increases with age, and a high proportion of older patients — 40 percent — report chronic pain (Davis 2000). Pain interferes with daily functioning in more than 70 percent of long-term care patients and individuals 70 years and older may be at the highest risk for insufficient pain treatment (Gloth 2001, Balducci 2003), followed by cognitive impairment (Schilling 2003). The increase in the elderly U.S. population has led to a higher share of resources devoted to the treatment of this population.

Health care professionals have outlined strategies and protocols for older Americans with pain, including a uniform standard of description for pain in the elderly. The goal is to enable age-specific studies on pharma-

### TABLE 3  First-line medications for neuropathic pain

<table>
<thead>
<tr>
<th>Medication</th>
<th>Beginning dosage (Maximum dosage)</th>
<th>Titration</th>
<th>Adequate trial length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>100–300 mg HS or 100–300 mg 3x/day (3,600 mg/day [1,200 mg 3x/day]); reduce if low creatinine clearance</td>
<td>Increase by 100–300 mg, 3x/day every 1–7 days as tolerated</td>
<td>3–8 weeks for titration, plus 1–2 weeks at maximum tolerated dosage</td>
</tr>
<tr>
<td>5% lidocaine patch</td>
<td>Maximum of 3 patches daily up to 12 hours</td>
<td>None</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Opioid analgesics (morphine sulfate)</td>
<td>5–15 mg every 4 hours, as needed (None with careful titration; consider evaluation by pain specialist at dosages exceeding 120–180 mg/day)</td>
<td>After 1–2 weeks, convert total daily dosage to long-acting opioid analgesic and continue short-acting medication as needed</td>
<td>4–6 weeks</td>
</tr>
<tr>
<td>Tramadol</td>
<td>50 mg 1x/day or 2x/day (400 mg/day [100 mg 4x/day; in patients &gt;75 years, 300 mg/day in divided doses)</td>
<td>Increase by 50–100 mg/day in divided doses every 3–7 days as tolerated</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Tricyclic antidepressants (nortriptyline, desipramine)</td>
<td>10–25 mg HS (75–150 mg/day; if blood level of parent drug and metabolite is &lt;100 ng/mL, continue titration with caution)</td>
<td>Increase by 10–25 mg/day every 3–7 days as tolerated</td>
<td>6–8 weeks with at least 1–2 weeks at maximum tolerated dosage</td>
</tr>
</tbody>
</table>

H5=at bedtime.

SOURCE: DWORKIN 2003

2003). In the event of partial response, combination treatment should be considered.

Since the issuance of the Fourth International Conference's guidelines in 2003, the U.S. Food and Drug Administration has approved duloxetine for diabetic peripheral neuropathic pain and pregabalin for neuropathic pain associated with diabetic neuropathy and postherpetic neuralgia.

### Guidelines for pain in the elderly

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Health care professionals have outlined strategies and protocols for older Americans with pain, including a uniform standard of description for pain in the elderly. The goal is to enable age-specific studies on pharma-
logical and care interventions and to widely disseminate assessment tools. The Comprehensive Geriatric Assessment (CGA), for example, has been shown to improve treatment of older patients by decreasing hospital stays and maintaining independence for as long as possible (Balducci 2003). The American Geriatric Society 1998 guidelines on the management of chronic pain were a significant advance in pain treatment for the elderly and their implementation contributed to increased pain management in the elderly population (Gloth 2001).

The guidelines, updated in 2002, redefined the term chronic pain in the older adult to persistent, in an effort to eliminate negative stereotyping. The new guidelines derive from evidence-based methodologies, and, like the APS guidelines, weight recommendations by quality and strength of evidence. Treatment assessment for the elderly is important, because few older patients have been included in clinical trials even for common pain relief medications. In 83 trials of nonsteroidal anti-inflammatory drugs, for example, only 2 percent of participants were over 65 years old (AGS Panel 2002).

Quality ratings range from Level I (evidence stemming from at least one properly randomized, controlled trial) to Level III (evidence from respected authorities), and strength ratings range from good evidence — “Clinicians should do this all the time” — to good evidence against the use of a recommendation, “contraindicated” (AGS Panel 2002). The guidelines include both clinical recommendations (for assessment of persistent pain, pharmacological treatment, and nonpharmacological strategies) and institutional recommendations (see Tables 3, 4a, and 4b in the article by Fine in this publication, on pages 48, 50, and 51 respectively.

**MCOS AND PAIN MANAGEMENT**

The AGS guidelines clearly indicate that cost implications must be considered in all treatment decisions. Not only should costs of treatment be considered, but costs of being untreated or undertreated should be considered. Chronic pain sufferers use health care resources extensively, as their visits to multiple specialists and emergency rooms and their diagnostic tests are more frequent than for patients without pain (Davis 2000). At the beginning of the 21st century, the costs of treatment and lost productivity due to chronic pain were estimated at $100 billion (Khouzam 2000). A review of pain management in the late 1990s found that the average patient had a history of three major surgeries and individual medical bills as high as $100,000 (McCarberg 1999). Disability programs and lost pro-

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**GUIDELINES**

**TABLE 4** Cancer pain management

- Develop a systematic approach to cancer pain management and teach patients and family caregivers how to use effective strategies to achieve optimal pain control.
- Provide cancer patients with a prescription for an analgesic medication (e.g., hydrocodone and acetaminophen, oxycodone with acetaminophen) and instruct patients to have the prescription filled, to take the medication if unexpected pain occurs, and to call their health care provider for an appointment to evaluate the pain problem.
- Base the initial treatment of cancer pain on the severity of the pain the patient reports.
- Begin a bowel regimen to prevent constipation when the patient is started on an opioid analgesic.
- Administer a long-acting opioid on an around-the-clock basis, along with an immediate-release opioid to be used on an as-needed basis, for breakthrough pain once the patient’s pain intensity and dose are stabilized.
- Do not use meperidine in the management of chronic cancer pain.
- Adjust opioid doses for each patient to achieve pain relief with an acceptable level of side effects.
- Avoid intramuscular administration because it is painful and absorption is not reliable.
- Use optimally titrated doses of opioids and maximal safe and tolerable doses of coanalgesics through other routes of administration before considering spinal analgesics.
- Monitor for and prophylactically treat opioid-induced side effects.
- Titrate naloxone, when in the rare instance it is indicated for the reversal of opioid-induced respiratory depression, by giving incremental doses that improve respiratory function but do not reverse analgesia.
- Provide patients and family caregivers with accurate and understandable information about effective cancer pain management, the use of analgesic medications, other methods of pain control, and how to communicate effectively with clinicians about unrelieved cancer pain.
- Provide patients with a written pain management plan.
- Clarify myths and misconceptions about pain and pain management and reassure patients and family caregivers that cancer pain can be relieved and that addiction and tolerance are not problems associated with effective cancer pain management.
- Use cognitive and behavioral strategies as part of a multimodal approach to cancer pain management, not as a replacement for analgesic medications.

*SOURCE: MIASKOWSKI 2005*
ductivity continue to contribute to the rise in costs (Berry 2000). Evidence that pain management saves costs can be weighed against these high expenditures; Treatment programs prevent the development of chronic pain, decrease or eliminate hospital stays, and reduce the number of hospital readmissions (Berry 2000).

**Barriers to optimal pain management**

Guidelines and the past 20 years of advances in pain management and research are critical steps in improving pain care and optimizing its management across the health care system. Yet, the best guidelines are only as good as their implementation (Gilron 2002).

Their implementation can be compromised as a result of a lack of resources, as a variety of conditions compete for health care dollars. Implementation of pain management guidelines is also impeded by attitudes and customs that inhibit optimal pain control. The Figure on page 30 depicts societal, health care system, and patient contributions to barriers found in best-practices pain management. Evidence-based medicine in particular, unless combined with strong incentives to incorporate it, can be hindered by entrenched beliefs and practices (Carr 2001).

**Opportunities for optimal pain management**

Regulatory initiatives, JCAHO accreditation standards, and legal issues all have combined to make comprehensive pain care highly important to MCOs (Lande 2001). MCOs also are implementing pain management programs that can improve outcomes and reduce costs (Davis 2000). Given this backdrop, the crucial nature of pain management must be articulated not only by MCOs, but also by other types of insurance companies and the government (AGS Panel 2002). Nevertheless, third-party payers need to be particularly attentive to the kind of financial incentives they are creating: Methods that seem cost-effective at first may not be so in the long term and may create needless pressure on patient care (AGS Panel 2002). In addition, costs and outcomes of various treatment strategies vary considerably, as does the subjective perception of pain, so there is a great need for further pharmacoeconomic and comparative studies (Zagari 1996).

There is an opportunity for MCOs to drive improvements in outcomes using best practices as the engine. For example, pain management programs increase patient satisfaction. In a 1999 study of nonpharmacologic interventions, 78 percent of the treatment group receiving cognitive-behavioral techniques and stress management were satisfied, while roughly 57 percent of the comparator minimal treatment group — which received only a manual for home study — were somewhat or very dissatisfied (McCarberg 1999). Effectiveness is improved, both clinically and in terms of cost, if patients with the potential for chronic pain are identified prior to the manifestation of symptoms (Davis 2000); the methods and instruments recommended in guidelines could potentially foster this assessment. Inadequately treated acute pain may lead to long-term pain issues; early and adequate control helps to eliminate such sequelae (Berry 2001). Guidelines for cancer pain management stress prevention of pain and early planning for its management rather than chasing it (Schmidt 1996, Miaskowski 2005); appropriate algorithms emphasize identifying pain-causing mechanisms before symptoms emerge.

Because the field of pain management increasingly relies on evidence-based guidelines, MCOs have an important role in their implementation. Evidence-based guidelines consist of recommendations and evaluations for optimal care, but their very nature, combined with the growing number of scientific studies to be reviewed, creates huge questions for MCOs. How best to monitor the effect of clinical guidelines? What is the best method for continually improving quality of care? It may be incumbent on pharmacy and therapeutics committees to play an increasingly larger role and insist on the provision of proof that a given intervention or method works for their institution. Grimshaw and colleagues (1995) note that significant resources are needed to develop optimal evidence-based guidelines, but that the investment can be gained back by small changes in process or outcome.

It also may be that evidence-based guidelines help to create a scenario in which guidelines can be implemented, assessed during a trial period, and the results of the trial period used to define best measures for future incorporation. MCOs need to define for themselves the process by which decisions regarding pain management treatment are made. This process should not be haphazard but one based on the best available evidence. Any policy that does not approach pain management in a rational, evidence-based manner carries with it the risk of patient suffering and the potential for increased — not decreased — costs.

Proper care must be instituted as quickly as possible, not delayed. MCOs and other health insurers must understand pain management and treat this field the same way that other specialties, such as cardiovascular medicine, are handled. Just as a noncardiologist would not be expected to make a complex decision regarding treatment of a complicated cardiovascular disorder, no one at the MCO or insurer should be making decisions regarding pain management care unless those individuals have proper credentials and experience. Such expertise could greatly help rather than hinder maximally effective, cost-efficient care.
Barriers to adequate pain management

**Documentation**
- No specific place to document pain assessment and/or ongoing treatment
- Lack of staff time to complete documentation
- No consistency in pain scales used within an institution

**Health care system**
- Concern that aggressive pain management will increase costs
- Reimbursement for high-tech pain treatment only
- Inconsistent reimbursement policies for pain treatment
- No reimbursement for certain analgesics (i.e., not on formulary, HMO restrictions)
- Lack of coordination of care across settings
- Lack of clarity about roles of professionals

**Laws/regulations**
- Confusion about the meaning of addiction and physical dependence
- Dosage unit limitations
- Requirements for use of specially issued government prescription forms
- Uninformed and overzealous monitoring of professional practice
- Belief (in some cultures) that pain is good
- Lack of knowledge of the adverse effects of pain

**Society**
- Fear of regulatory sanctions
- Lack of positive statements about the important medical usefulness of controlled substances
- Regulator’s confusion about the role of opioids in pain treatment

**Health care professionals**
- Controversy about use of opioids for chronic noncancer pain
- Belief that patients are not authority about their pain
- Absence of role models in clinical practice
- Fear of regulatory scrutiny
- Lack of thorough and frequent re-evaluation of patient’s pain status
- Failure to assess pain
- Lack of access to pain management experts
- “Meaning” of pain
- Lack of knowledge
- Lack of basic and ongoing education
- Fear of regulatory scrutiny
- Inconsistent use of pain scale
- Low priority
- Low priority
- Takes “too much time”

**Patients and families**
- Financial drain
- Inability to work
- Cost of meds
- Being “good” and not complaining
- If pain controlled, life may be shortened
- Fears
- Addiction
- Side effects
- Pain = death and worsening of the disease
- Past negative experiences with pain and pain management
- Low expectations
- Loss of insurance

**Inadequate pain management**
- Lack of accountability for pain management
- Lack of clear mandates/standards/expectations
- Pharmacies may not stock opioids
- Fragmentation of care
- Lack of access to comprehensive pain management facilities
- Lack of knowledge
- Recipient of incorrect knowledge
- From health care professionals
- Need to “save” strong meds for later
- Erroneous beliefs
- Reporting pain may distract from treatment of illness
- Pain medications may make people sleepy
- Gender and age variations
- Cultural variations
- Spiritual beliefs

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Though many questions remain regarding best pain management practice, the availability of treatment guidelines should guide MCOs and other third-party entities in the development of pain management treatment strategies, and the process by which decisions are made should be both clearly defined and transparent. Perhaps most importantly, guidelines should lead to collaboration among health care providers, health care insurers, and patients, in helping to further define appropriate pain management treatment. Much work needs to be done, not only in developing these standards but also in their implementation and reassessment.

REFERENCES
It is no secret that pain costs money. Ubiquitous and undertreated, pain remains a significant problem in the United States and poses a considerable financial strain on MCOs. Chronic pain conditions are common in the U.S. population. About 9 in 10 Americans regularly suffer from pain, and significantly, pain is the most common reason individuals seek health care (APS 2000; Arthritis Foundation 1999). Not surprisingly, some managed care plans find that the cost impact of chronic pain problems rivals those of typical chronic conditions. One HMO that studied its own membership found pain management to be the most costly of all chronic conditions (Fishman 1997).

Health care providers’ obligation to act in the best interest of their patients might include the use of opioid medication to treat patients with symptoms of pain. Though many types of pain can be addressed by nonopioid interventions, for some patients, opioid analgesics are the most effective way to treat their pain. In fact, they are often the only option that provides significant relief. Because objective signs are not always present, the most difficult decision facing physicians who treat patients with chronic pain is whether and how to prescribe opioid therapy (Ballantyne 2003).

Although diagnoses are improving and treatment options are expanding, the management of pain using opioids is hampered by a number of factors, including stigma about medication abuse; changing and generally wary attitudes about medical opioids; insufficient education among health care providers about opioids and addiction; and concerns about regulatory oversight and intervention. It must be acknowledged that the recent prescription-drug abuse problem has arisen, at least in part, due to a redistribution of abuse from nonprescription to prescription drugs (Table 1). As a result, many physicians have become reluctant to write prescriptions for Schedule II or III drugs due to heightened federal vigilance, and will prescribe alternative medications that

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**SUMMARY**

Opioids are highly effective for many types of chronic noncancer pain, but their use has been stigmatized by concerns about addiction and regulatory scrutiny. Many stakeholders in the managed care community are not educated fully about proper diagnosis, treatment, and monitoring of pain and the use of opioids to relieve symptoms. Informed diagnoses, careful prescribing and monitoring of opioid use, and education about addiction and addictive substances are key components of a pain management regimen.

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1San Diego-based Bill H. McCarberg, MD, is founder of the Chronic Pain Management Program for Kaiser Permanente. He was on the board of directors of the American Pain Society and is on the board of the National Pain Foundation. He is president of the Western Pain Society and assistant clinical professor (voluntary) at the University of California–San Diego School of Medicine. McCarberg holds memberships in the American Academy of Family Physicians, the American Academy of Pain Medicine, and the International Association for the Study of Pain. The recipient of several awards, including the Shilling Compassionate Care Award, he was named the Highest Rated Physician by Member Appraisal of Physician Services at Kaiser Permanente in 1998. He also received the Elizabeth Narcessian award for leader in the field of pain education from the American Pain Society. He has given more than 200 presentations on pain management issues and has authored or coauthored several publications. McCarberg received his medical degree from Northwestern University Medical School.
they perceive to be less scrutinized, even if they are less effective or potentially more toxic (Fishman 1997).

The core of the issue, then, is: Both the government and the health care community have an obligation to ensure the availability of opioids while implementing a system that prevents abuse, trafficking, and diversion of opioids and other controlled substances. Governing bodies, advocacy groups, and the medical community at large recognize that effective pain management is integral to quality medical care, that pain must be treated aggressively, and that the failure to do so represents a lapse in responsible patient care. With this mandate, and with clinical evidence in short-term use that supports the safety and efficacy of opioids, long-term prescribing is on the upswing. Nevertheless, medications such as methadone, oxycodone (OxyContin), hydrocodone, and hydromorphone (Dilaudid) have received increased government and media attention over the past few years, because their medical use has been accompanied by an increase in reported drug abuse and dependence, adverse medical events, and pharmacy robberies.

Conflicting dynamics and the balance between patient care and provider risk characterize any discussion of managing pain using opioids. This article discusses how physicians, formulary committees, and managed care decision makers can provide the highest quality care for their patients while protecting against abuse and regulatory intervention. Informed diagnoses, appropriate prescribing and careful monitoring, and education about addiction and addictive substances are the key components of a pain management regimen involving opioids.

**CLINICAL CASE FOR OPIOIDS**

The past decade has brought acceptance among pain specialists and many other physicians who treat chronic pain that opioids are an integral component of the management of chronic noncancer pain when other approaches have failed and when quality of life is poor because of the pain (Gardner-Nix 2003). Ample testimony that opioids often are the most effective analgesic available can be found in the literature, even in light of the more varied pain relievers coming out of pharmaceutical companies. Several randomized controlled studies have demonstrated the efficacy of opioids in a variety of noncancer conditions (Arkinstall 1995, Moulin 1996), including postherpetic neuralgia (Watson 1998) and lower back pain (Jamison 1998). These studies were among 16 studies overviewed by Ballantyne and Mao, who found that 15 of them showed significant analgesic efficacy of opioids in the treatment of chronic pain, including neuropathic pain (Ballantyne 2003).

As with any medication, there are caveats with the prescription of opioids. Awareness of this information varies but generally tends to be lacking in the medical community. One important point is: What happens when opioids are given to someone in pain will be different from what happens when they are given to someone not in pain. For example, one concern is the potential for respiratory depression in patients taking opioids; yet this phenomenon is seen in studies of volunteers who are not in pain, whereas respiratory depression is rare when appropriate regular doses are used in chronic pain (McQuay 1999).

The clinical message is that opioids need to be titrated against pain: Excessive doses, or initial doses in opioid-naive patients, can cause respiratory depression. Titration can be done with long-acting, sustained-release opioids, or through some short-acting opioids, and then con-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Illicit drug use</th>
<th>12 or older</th>
<th>Age 12–17</th>
<th>Age 18–25</th>
<th>26 or older</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S. population</td>
<td>235,143,000</td>
<td>24,753,000</td>
<td>31,024,000</td>
<td>179,366,000</td>
</tr>
<tr>
<td>(% of total 12+ population)</td>
<td>(100.0)</td>
<td>(10.5)</td>
<td>(13.2)</td>
<td>(76.3)</td>
</tr>
</tbody>
</table>

Numbers and percent of population of users

| Any illicit drug use | 35,132,000 | 5,495,166 | 11,013,520 | 18,654,064 |
| (% of all users, 12 or older) | (15.6) | (31.3) | (53.1) | (50.6) |
| Illicit pain reliever use | 10,992,000 | 1,881,228 | 3,536,736 | 5,560,346 |
| (% of all users, 12 or older) | (17.1) | (32.2) | (50.6) | (50.6) |

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verted to a sustained-release form when a maintenance dose is achieved. Once an opioid is chosen, the dose is increased to balance improved pain control and function against side effects.

Side effects include persistent nausea and/or constipation, excessive sweating, itching, peripheral edema, and sexual dysfunction. These effects should not mean limiting an opioid, but changing the choice or administration of the opioid (Gardner-Nix 2003). Because, clinically, opioids are titrated to effect, one would not expect to see much difference in efficacy among opioids. Recent discoveries of genetic polymorphism to the opioid receptor demonstrate variability among opioids and patients’ responses to them; no clinical evidence is available of such differential efficacy, however. Similarly, though in some patients a change of opioids (at the same level of analgesia) can reduce adverse effects, specific guidelines based on carefully performed studies are not available (McQuay 1999). Using standard equianalgesic tables could overestimate conversion doses, but equianalgesia never has been studied in the population where it is most important: chronic pain patients. Therefore, when switching to an alternate opioid, a 10 to 20 percent reduction below equianalgesic recommendations should be made.

Additionally, there is little difference among most opioids in speed of onset and duration of effect (the notable exceptions being fentanyl and methadone). Faster onset and longer effect are achieved by changing the route of administration or formulation. Further, there are few reports of long-term toxicity from long-term opioid use in chronic pain. The notable exception is damage to the neuroendocrine system, especially sexual gonadotropins. When opioids are used responsibly at stable doses, a balance between pain control and side effects can be established, and these drugs can be considered safer in some clinical contexts than other analgesics, such as tricyclic antidepressants and nonsteroidal anti-inflammatory agents.

## Responsibilities and Liabilities

Given that clinicians need the availability of opioids, and law enforcement wants to monitor and appropriately restrict this availability, these two entities share the responsibilities for ensuring that opioids are available to the patients who need them, and for preventing these drugs from becoming a source of harm or abuse. A number of recent policy statements from advocacy groups and regulatory bodies reflect the current consensus that pain is undertreated, and that when properly prescribed and monitored, opioids are a viable option for treating chronic and acute pain.

Several relevant themes run through these documents. One is a discussion of physician responsibilities and liabilities in the prescription of controlled substances for treating pain. Health care professionals should not be timid about prescribing opioids and other controlled substances where they are deemed appropriate. Sanctions should be enacted only where negligence or abuse are suspected. For example, the *Model Policy for the Use of Controlled Substances for the Treatment of Pain*, published in 2004 by the Federation of State Medical Boards (FSMB), makes it clear that providers have the right to prescribe opioids. They also have a responsibility to minimize the potential for the abuse and diversion of controlled substances. This responsibility entails an understanding about addiction and addictive substances, as well as the appropriateness of the prescription of opioids, the selection of a particular opioid drug or drugs, and the determination of dosage and interval of medication administration. These can be made properly only with a full and detailed understanding of a particular clinical case (FSMB 2004).

Despite this policy guideline and its 1998 precursor, the successful implementation of state medical board pain policy varies among jurisdictions. Table 2 shows

### TABLE 2

Number of states with policy language having potential to impede pain management

<table>
<thead>
<tr>
<th>Negative provisions</th>
<th>Number of states</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids are considered a treatment of last resort</td>
<td>9</td>
</tr>
<tr>
<td>Medical use of opioids is implied to be outside legitimate professional practice</td>
<td>14</td>
</tr>
<tr>
<td>The belief that opioids hasten death is perpetuated</td>
<td>15</td>
</tr>
<tr>
<td>Physical dependence or analgesic tolerance is confused with “addiction”</td>
<td>18</td>
</tr>
</tbody>
</table>

**Medical decisions are restricted:**

| Restrictions based on patient characteristics                                      | 5                |
| Mandated consultation                                                                | 11               |
| Restrictions regarding quantity prescribed or dispensed                             | 10               |
| Length of prescription validity is restricted                                       | 7                |
| Practitioners are subject to additional prescription requirements                   | 3                |
| Other provisions that may impede pain management                                    | 15               |
| Provisions that are ambiguous                                                       | 33               |

**Source:** PAIN & POLICY STUDIES GROUP 2004
negative policy language that could impede pain management.

A consensus statement issued in 2004 by the American Pain Society (APS), American Academy of Pain Medicine, and American Society of Addiction Medicine, titled The Rights and Responsibilities of Healthcare Professionals in the Use of Opioids for the Treatment of Pain, recommends that health care professionals use clear and reasonable medical judgment to establish that a pain state exists and to determine whether opioids are an indicated component of treatment (APS 2004). Health care professionals who practice medicine in good faith and who use reasonable medical judgment regarding the prescription of opioids should not be held responsible for the willful and deceptive behavior of patients who successfully obtain opioids for nonmedical purposes. Conversely, interventions are appropriate to correct the practices of professionals who consistently fail to recognize addictive disorders, medication misuse, or medication diversion in their patients.

Another theme in many of these documents is the recognition of a lack of education among primary care providers and MCOs about pain. Pain Assessment and Treatment in the Managed Care Environment, an APS position statement, notes: “There is an insufficient level of credentialed experts among managed care PCPs [primary care providers] to provide appropriate care for most patients with chronic pain conditions. MCOs should provide information and management activities that help PCPs make determinations about consultations or treatment” (APS 2000). When treatment is not effective, early access to appropriate specialists can result in improved outcomes.

In particular, this paper states that distinguishing diagnoses between chronic and acute pain can be a troublesome area for some primary care providers; chronic pain problems tend to be qualitatively different from acute pain, not only temporally but also in character and response to treatment (Merskey 1994). Therefore, it is appropriate for plans to develop policies and strategies that can facilitate identification of members with chronic noncancer pain conditions or syndromes; appropriate referral of such members to specialized providers; education and assistance to primary care providers in accomplishing these objectives; and development of disease state management programs for chronic pain similar to those designed for other chronic diseases.

A BETTER UNDERSTANDING OF ADDICTION

A key area in which education is lacking among primary care providers is addiction in the context of opioid medication prescriptions (Haack 2002). Physicians who are willing to prescribe opioids to challenging and psychosocially stressed patients, or those with a history of substance addiction, assume an additional obligation to understand the risks and management of addictive disease. Addiction to opioids can occur despite appropriate opioid therapy for pain in some susceptible individuals, and a decision whether to prescribe opioids can be difficult, particularly in patients with concurrent addictive disorders or with risk factors for addiction, such as a personal or family history of addictive disorder.

Health care providers must be able to distinguish between addiction, physical dependence, and tolerance. These are discrete phenomena that often are confused, the key distinguishing factor being that physical dependence on and tolerance to prescribed drugs do not constitute sufficient evidence of a psychoactive substance use disorder or addiction. Although this might be the case with alcohol and other abusable substances, it is not so with opioids. These are normal responses that often occur with the persistent use of certain medications. Currently accepted definitions have been proffered by the APS (2001):

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors such as impaired control over drug use, compulsive use, continued use despite harm, and craving (often referred to as the “four Cs” of addiction).

Physical dependence is a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, or administration of an antagonist.

Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time.

Addiction, unlike tolerance and physical dependence, is not a predictable drug effect, but represents an idiosyncratic adverse reaction in biologically and psychosocially vulnerable individuals. Most specialists in pain medicine and addiction medicine agree that patients treated with prolonged opioid therapy usually develop physical dependence, and sometimes develop tolerance, but do not usually develop addictive disorders (APS 2001).

Physicians can best identify addiction in the course of opioid therapy of pain after the pain has been brought under adequate control. One problem is that an individual’s behaviors that suggest addiction sometimes are simply a reflection of unrelieved pain or other problems unrelated to addiction. These behaviors may include the inability to take medications according to an agreed-
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upon schedule, taking multiple doses together, frequent reports of lost or stolen prescriptions, doctor shopping, isolation from family and friends, and/or the use of non-prescribed psychoactive drugs in addition to prescribed medications. Good clinical judgment must be used in determining whether the pattern of behavior signals the presence of addiction or reflects a different issue.

A related concern is pseudoaddiction, a term used to describe patient behaviors that can occur when pain is undertreated. Patients with unrelieved pain can become focused on obtaining medications and might “clock watch” or otherwise seem inappropriately fixated on drugs. Pseudoaddiction often is difficult to distinguish from true addiction, but usually shows deteriorating physical and psychosocial functioning despite dose increases.

SCREENING AND MONITORING

Clearly, identifying patients at highest risk for addiction or medication abuse, or otherwise inappropriately responding to opioid therapy is a critical task for physicians, pharmacists, and managed care professionals. A number of screening tools are available to assist the provider in this regard, although most are geared primarily toward assessing patients with a history of alcohol abuse or dependence, or with a history of illicit drug use. Pain advocacy groups emphasize that the purpose of screening is not to deny patients opioids for pain, but to identify the small subgroup at higher risk for addiction to do a more a detailed assessment and more careful monitoring. Ultimately, intimate understanding of a particular patient’s needs, history, and response to therapy are all critical in choosing the correct course of treatment. The primary care provider might find that a referral to a pain center or addiction specialist is necessary.

Established screening tools include SISAP (Screening Instrument for Substance Abuse Potential), a five-item test that helps the clinician to categorize patients into lower or higher risk of abusing prescribed opioids (Coombs 1996). The test requires that the physician already know the patient or have collateral information to confirm the accuracy of the answers. Similarly, the CAGE-AID questionnaire is a quick screening tool to assess the risk of serious alcohol or drug problems. Patients that show an inclination toward substance abuse or addiction can be considered to be at a higher risk for abusing or misusing their prescription medication (Ewing 1984).

A new tool is the Screener and Opioid Assessment for Patients with Pain (SOAPP), developed by Inflexxion, the National Institute on Drug Abuse, and Endo Pharmaceuticals (Butler 2004). Created in consensus with 26 pain and addiction experts, SOAPP is a self-administered, pencil-and-paper questionnaire that asks patients a series of questions regarding their pain, drug history, family history of substance use, and other topics. The answers can offer insight into which patients could be at risk for drug abuse. Conversely, SOAPP can help clinicians who are reluctant to prescribe opioids to realize that many patients may receive these medications with little likelihood of addiction.

Diversion of prescription opioids is another concern for health care professionals. Law enforcement, pharmacy theft data, retail distribution of controlled substances, and Medicaid and prescription monitoring programs (PMPs) are useful sources for tracking prescription diversion. Typically, PMPs collect prescribing and dispensing data from pharmacies, conduct review and analysis of the data, and make them available under certain circumstances to regulatory and law enforcement agencies, as well as practitioners. To date, 21 states have implemented PMPs to monitor the prescribing of certain controlled substances and detect illicit prescribing and dispensing (Pain and Policy Studies Group 2005). Additionally, the National All Schedules Prescription Electronic Reporting Act of 2003 established funding for a nationwide electronic database to monitor the dispensing of Schedule II, III, and IV medications.

PMPs are undergoing re-evaluation and restructuring as new technology is developed and implemented. Many states recently have begun to use electronic data transmission (EDT) systems, which have proven to be comprehensive and effective means of controlling prescription-drug diversion. Current data show a trend away from use of special government-issued prescription forms and toward electronic monitoring systems (Figure).

EDT systems also are attractive because they alleviate some of the potentially negative consequences associated with PMPs. Overall, statistics show that the implementation of PMPs typically leads to a decrease in the prescribing of Schedule II controlled substances. Some physicians would rather avoid the extra paperwork involved in prescribing controlled medications and substitute inappropriate nonregulated drugs; others worry about being labeled as an overprescriber, or feel that drugs needing a special prescription must be more dangerous and should be avoided at all costs. Patients report that they fear loss of confidentiality and stigmatization by having their names tracked, as well as an increased difficulty in obtaining needed medications because many physicians will not prescribe drugs that are monitored by a PMP. EDT programs offer potential solutions to these issues in that they do not require the use of government-issued prescription forms, and make prescription monitoring transparent to the prescriber through the periodic
transfer of prescription data from pharmacy computers to the relevant state agency (Fishman 2004).

Unfortunately, the Drug Enforcement Administration currently prohibits the electronic transmission of controlled substance prescriptions, but it is working on a system for secure electronic transmission of Schedule II drugs, which it calls the Electronic Prescriptions for Controlled Substances project. High levels of security and accuracy are the mandates for this system, which would involve issuing digital certificates that function as authentication of a practitioner’s authority to prescribe and digitally sign prescriptions for controlled substances (DEA 2003).

SUMMARY

Health care professionals, law enforcement personnel, and regulators all share a responsibility for ensuring that prescription-pain medications are available to the patients who need them, and for preventing these drugs from being misappropriated or misused. All stakeholders must ensure that accurate information about both the legitimate use and the abuse of opioids is made available, and efforts are ongoing in this regard on several fronts. Nonetheless, the fact remains that chronic noncancer pain is widely undertreated, and it is likely that heightened scrutiny of physicians and sanctions for inappropriate prescribing will have an adverse effect on patient care. In considering the use of opioids in pain management, currently the best guide for physicians is sound clinical judgment based on the patient’s specific pain condition and any comorbid disorders. Formal policies may assist in making rational determinations that maintain patients’ access to pain treatment and concurrently attempt to control diversion and abuse.

REFERENCES


During the past 2 decades, advances in drug formulations and innovative routes of administration have resulted in improved patient adherence to their therapeutic regimens and improved pharmacologic responses. Refined understanding of drug transport across tissues has led to the development of transdermal and transmucosal delivery systems that offer the advantage of ease of administration. Also, the potential for greater flexibility in a variety of clinical situations exists that would bypass the need for parenteral interventions, a particular benefit for children. The availability of various routes of analgesic administration can add to the sometimes perplexing decisions associated with selecting an appropriate, efficacious, and cost-effective regimen to manage chronic pain. The primary goals of therapy are “to achieve adequate pain relief safely within an acceptable time frame, to minimize the side effects of treatment, and to provide ongoing analgesia by the most convenient and least noxious means available” (WHO 1996). In the following pages, various delivery systems will be discussed along with their advantages and potential disadvantages.

**ORAL DELIVERY SYSTEMS**

For reasons of convenience and cost-effectiveness, the oral route is the preferred route of analgesic administration when a patient is physically able to ingest oral medications (Jacox 1994). Concentrated dosage forms, like the controlled-release oral opioid preparations, are among the most important recent innovations in analgesia treatment. Due to their long duration of action, these preparations lessen the severity of pain that may be experienced at the end of the dosing interval and often allow ongoing analgesia during sleep. For example, the morphine sulfates MS Contin and Oramorph SR, as well as oxycodone (OxyContin), provide 8 to 12 hours of analgesia with a single dose. Kadian and Avinza are controlled-release morphine preparations that sustain therapeutic plasma levels of the drug for 12 to 24 hours, respectively, with a single dose.
Immediate-release formulations

Immediate-release formulations have been developed for the treatment of moderate to severe pain and have short-acting (3 to 4 hours) analgesic activity. These medications also are given as breakthrough pain coverage in patients receiving prolonged therapy. Analogic effects of short-acting oral opioids, such as morphine, hydromorphone, codeine, and oxycodone, typically begin within a half hour of administration and last for approximately 4 hours. The dosing interval of these drugs is usually 4 hours. Commonly available immediate-release formulations are immediate-release morphine sulfate (MSIR) and immediate-release oxycodone (OxyIR). Morphine has a terminal elimination plasma half-life of about 3.1 hours. In contrast, methadone possesses a variable terminal plasma half-life averaging approximately 24 hours and an oral bioavailability of 50 to 80 percent. It is often used as an oral analgesic in the treatment of cancer pain. Because it has a lower first-pass metabolism than morphine, methadone is approximately twice as potent when administered orally (bioavailability is 50 to 60 percent). Hydromorphone, a potent mu agonist, has a terminal plasma half-life of 2.6 hours. It is approximately 50 percent bioavailable when given orally.

Controlled-release formulations

For longer-lasting analgesia, several formulations have been developed that provide for a slow release of morphine. Some long-acting preparations use a hydroxyethyl cellulose and hydroxypropyl methylcellulose matrix to surround the active drug. The cellulose then slowly dissolves in the stomach and small intestine, resulting in a sustained release of active drug. Bioavailability of these slow-release preparations is the same as that of immediate-release preparations, but time-to-peak plasma drug concentrations (Tmax) is longer and peak plasma concentrations (Cmax) is decreased. Examples of slow-release opioid preparations are MS Contin and OxyContin. While MS Contin and OxyContin need to be administered every 12 hours, Kadian can be administered once every 12 to 24 hours. A long-acting opioid preparation given on a scheduled (around-the-clock) basis is preferred for providing analgesia in patients who experience constant pain. Controlled-release formulations like morphine or oxycodone start acting within 1 hour, peak in 2 to 3 hours, and last for approximately 12 hours. These formulations usually are prescribed in 12-hour intervals; a small subset of patients on 12-hour controlled-release formulations (10 to 20 percent) may require administration every 8 hours, however.

The main problem with the oral route is first-pass metabolism of opioids in the liver. All opioids given orally are absorbed via the gastric and duodenal mucosa and then transported to the liver via the portal venous system. In the liver, these medications undergo first-pass metabolism before entering the systemic circulation. This has a major impact on the systemic plasma concentrations of drugs. First-pass metabolism decreases the bioavailability of morphine to 30 to 40 percent, methadone to 50 to 80 percent, and oxycodone to 60 to 87 percent of the total administered dose. For example, the dose of an opioid given orally to a patient with cancer pain must be 3 times the intravenous (IV) or subcutaneous (SC) dose of morphine and twice the parenteral dose of methadone (Portenoy 1994).

Oral transmucosal (sublingual, buccal) administration

Analgesics given sublingually (under the tongue) or buccally (between the mucous membranes of the cheek and the gum) are absorbed rapidly. The sublingual administration of opioids is particularly beneficial in the patient with cancer who is unable to tolerate oral administration because of nausea/vomiting or dysphagia (Weinberg 1988). It also may be attractive in patients who cannot receive parenteral opioids because of lack of venous access, emaciation, or coagulation defects. Importantly, the sublingual venous drainage is systemic rather than portal.

Hence, medications given via this route avoid hepatic first-pass metabolism. The sublingual route also offers the potential for more rapid absorption and, hence, quicker onset of action. In addition, the higher pH of the oral cavity improves the absorption of opioids. Lipophilic drugs are better absorbed than are hydrophilic drugs, which explains why the absorption of methadone (35 percent), fentanyl (51 percent), and buprenorphine (56 percent) are greater than absorption of morphine (22 percent).

Simplicity is the major advantage of sublingual drug administration, as it necessitates little expertise, preparation, or supervision. The side effects are limited to a bitter taste and, in some instances, a burning sensation. Because of its higher bioavailability, rapid onset of action and desirable side-effect profile, fentanyl has been the most commonly used opioid via the buccal route in the United States. The overall observed bioavailability of transmucosal fentanyl is approximately 50 percent of the total dose because a fraction of the dose gets absorbed through both the oral mucosa as well as the gastrointestinal tract. Transmucosal fentanyl may become a very useful tool in the management of breakthrough pain in cancer patients who are unable to swallow tablets or capsules.

Breakthrough pain is a moderate to severe flare-up of otherwise controlled pain.
RECTAL ADMINISTRATION

Rectal administration may be a simple alternative when the oral route is not possible because of vomiting, obstruction, or altered consciousness. Its principal advantage is that it is independent of gastrointestinal tract motility and rate of gastric emptying (Hanning 1990). Given the well-known propensity of opioids for slowing gastric emptying and their ability to induce nausea and vomiting, this route may be of considerable importance with the opioid analgesics. In addition, for patients who have an ostomy, opioids may be administered directly into the ostomy by the patient, nurse, or family member (Maloney 1989).

The most suitable analgesic for the rectal route is the suppository, although if necessary, any tablet that is used for oral administration can be used rectally. The most commonly available opioid analgesics in suppository form in the United States are morphine, hydromorphone, and oxymorphone. Other opioids (e.g., oxycodone, codeine, and meperidine) also are readily absorbed rectally. Hydromorphone is available in 3-mg suppositories, morphine in 5-, 10-, 20-, and 30-mg suppositories, and oxymorphone in 5-mg suppositories (McCaffery 1992). It has been shown that analgesics given via the rectal route provide analgesia equivalent to the oral dose. Therefore, the usual recommendation for initial doses of morphine and most other opioids given rectally is the same dose as that given orally.

PARENTERAL DRUG DELIVERY

In most cases, acute or chronic pain can be managed adequately with oral analgesics. Nevertheless, certain circumstances (nausea or vomiting, difficulty swallowing, cognitive impairment, disruptive gastrointestinal function, rapidly escalating pain) may necessitate administration via other routes (Cherny 1993). The most commonly used parenteral routes of delivery are IV, SC, intramuscular (IM), intrathecal, and epidural.

Intravenous administration

An IV bolus provides the most rapid onset of pain relief. This route of administration is available for patients whose pain cannot be controlled by a less invasive route. Among the analgesics available in IV solution, the most commonly used in the United States for treating pain include morphine, hydromorphone, and fentanyl. Meperidine, a semisynthetic opioid, is not commonly used for long-term IV infusion. The first-order metabolite of meperidine, normeperidine, may accumulate with repetitive dosing, especially in the presence of decreased renal function. Increased normeperidine plasma levels may cause central nervous system irritability, including myoclonus and seizures. Morphine is available for administration as an IV solution in several concentrations ranging from 1 mg/mL to 25 mg/mL for infusion. Hydromorphone is available as a solution for IV injection in 1-, 2-, 4-, and 10-mg/mL. Fentanyl and sufentanil are both highly lipid soluble and thus highly potent synthetic opioids. Fentanyl is approximately 100 times more potent than morphine, and sufentanil is approximately 1,000 times more potent. Historically, the morphine and sufentanil have been used primarily for anesthesia intraoperatively; their use in critical care and other settings has increased in recent years, however, due to the recognition of potentially favorable pharmacokinetic and pharmacodynamic properties. In addition, they have been used extensively in IV continuous infusions to manage cancer pain in patients who are unable to tolerate other opioids, such as morphine.

The major disadvantage of this route is that it requires continuous IV access, using devices such as a Port-a-Cath or other types of in-dwelling central or peripheral catheters. Any in-dwelling IV catheter can serve as an entry port for infection, and thus requires skilled nursing attention if the patient is unable to care for the catheter access. Significant costs are incurred when placing a permanent IV access, preparing the opioid solution for injection by the pharmacist, and administering the infusion via an external pump. For outpatients, having an IV opioid infusion for pain control may require outpatient nursing support, which also may incur significant costs. For these reasons, the IV route is used only when less invasive routes are unavailable or inappropriate.

Subcutaneous administration

The SC route usually is used for patients requiring parenteral analgesics who do not have in-dwelling IV access (Storey 1990). When a drug is given subcutaneously, it is absorbed beneath the skin into the connective tissue or into fat under the dermis. The preferred sites for SC injections are the chest, abdomen, upper arms, or thighs (Swanson 1989). Although the SC route is most commonly used for intermittent, bolus injections, it also can be used for continuous infusions. In the latter case, the shaved site is sterilized with povidone iodine and the needle is held in place by a bandage. A clear plastic occlusive dressing is then applied to cover the needle, and a loop of tubing is secured with adhesive tape. The injection site needs to be changed weekly or as needed.

A disadvantage of the SC route is the potential for delayed systemic absorption arising from drug solubility and local vasoconstriction (Moulin 1991). Another limiting factor is the volume of fluid that can be injected per hour. Infusion rates of 2 to 4 mL per hour have been found to be satisfactory without causing pain at the infusion site (Bruea 1987). Therefore, concentrated solu-
tions of morphine or hydromorphone are commonly used.

**Intramuscular administration**

As a rule, the IM route is not recommended for pain management, because such injections often are painful and analgesic absorption is variable and unpredictable (O’Neill 1996). If a drug is given intramuscularly, it is injected most often into the deltoid or vastus lateralis muscles.

**Neuraxial (epidural and intrathecal) administration**

Neuraxial administration refers to the administration of medications into the spaces or potential spaces surrounding the spinal cord or cauda equine (Glynn 1988). Neuraxial administration allows for the utilization of lower doses of medication due to increased concentrations of the opioid at target opioid receptors in the spinal cord. Thus, the primary indication for neuraxial opioid administration is for patients who are unable to tolerate systemic opioid therapy yet experience an analgesic effect. A long-term epidural catheter also can be inserted and tunneled subcutaneously for intermittent bolus dosing or for continuous infusion via an external pump. This form of opioid administration is used to control pain following a variety of surgical procedures and for cancer pain. The two opioids most commonly used via this route are morphine and fentanyl. A skilled health care team that is familiar with the benefits and risks of this type of therapy should be responsible for maintaining such patients.

Deciding between epidural versus intrathecal placement or external versus implantable pumps to deliver the opioid is based on multiple factors, including duration of therapy, type and location of the pain, disease extent and central nervous system involvement, opioid requirement, and individual preference (Krames 1993). Chronic epidural analgesic administration generally is reserved for patients with limited function and a prognosis of less than 3 months (Ferrer-Brechner 1989). Epidural delivery involves the administration of the drug via an external pump, requires skilled nursing personnel for maintenance, and may carry a higher risk of infection compared with implantable systems. Implantable intrathecal catheters are tunneled to an internalized programmable pump that delivers the opioid (usually morphine), according to a predetermined effective dose. Intermittent bolusing, variable-rate programs, and simple continuous infusions may be used and adjusted to patient needs. Pharmacoeconomic analyses have determined that, in cancer patients, a remaining life span of 3 to 6 months favors an implanted intrathecal catheter over external epidural administration (Reisfield 2003).

The neuraxial route provides effective, prolonged, segmental analgesia. The benefits of this method of opioid administration reflect the fact that smaller doses can be used. The most common adverse effects of neuraxial opioid administration are nausea and vomiting, pruritis, sedation, and respiratory depression, but the incidence and severity of these effects are less than those experienced in patients receiving systemic opioids. In addition, because most opioid-induced adverse effects are dose-related, the incidence of their occurrence can be further reduced through slow dose titration, frequent patient assessments, and avoidance of concomitant use of other central nervous system depressants such as systemic opioids, antiemetics, and benzodiazepines. The complications and side effects associated with the neuraxial approach also can be due to surgical complications like infections and/or bleeding at various sites (intrathecal, epidural, pump pocket, pump reservoir, and/or incisional sites), or complications related to device malfunction such as catheter kinking, obstruction, disconnection, shearing, granuloma formation, or migration of the catheter (Hassenbusch 1995). Vigilance and meticulous attention to details will help prevent catastrophic pump-filling errors.

**Patient-controlled analgesia**

Patient-controlled analgesia (PCA) is a technique in which the patient controls the amount of analgesia received (Kerr 1988). PCA provides the important advantage of allowing the patient to administer the analgesic simultaneously with the perception, or anticipated perception, of pain. PCA usage minimizes the incidence of sedation because sedated patients are unable to continue medication administration. The push of a button releases a pre-set dose of analgesic (typically opioids) to be delivered into the IV/SC route of the patient. The medication is delivered as long as the lockout interval (a predetermined time between doses) has not been exceeded. PCA is most often used for the IV administration of opioid analgesics for severe acute pain, such as following a major surgical procedure. Short- and long-term management of cancer pain by PCA also has been shown to be safe and effective (Baumann 1986).

The SC route usually is used in conjunction with a PCA device such as the CADD pump, which provides the patient with better control over the analgesia than does a continuous infusion alone (Ferrell 1992). The bioavailability of hydromorphone using a PCA device has been shown to be approximately 80 percent in cancer patients when administered via the SC route. Steady-state plasma hydromorphone concentrations have been reported to be
achieved within 24 hours. There is a high degree of effectiveness in providing adequate analgesia to cancer patients with a low rate of skin infections (1 of 117 patients in one study [Swanson 1989]) using SC PCA opioids. The main advantages of SC over IV PCA is that there is no need for vascular access, changing sites can be accomplished easily, and problems associated with in-dwelling IV catheters are avoided (Citron 1986).

TRANSDERMAL DRUG DELIVERY

For patients unable to take oral medications, the transdermal route is a noninvasive option for maintaining continuous plasma concentrations of opioids (Calis 1992). With the transdermal route, the drug is absorbed through the surface of the skin. At present, fentanyl (Duragesic patch) is the only opioid medication available in this form. Fentanyl is available in a transdermal drug delivery system that provides continuous opioid administration without pumps or needles. Transdermal fentanyl may be given to opioid-tolerant patients with stable chronic pain who can benefit from continuous opioid administration (Southwell 1984).

Fentanyl reservoir system

This delivery system consists of a reservoir of fentanyl and alcohol that contains a 3-day supply of fentanyl. The drug reservoir is separated from the skin by a permeable membrane that controls the rate of release of fentanyl from the reservoir. A fentanyl-saturated adhesive layer holds the system in place and administers a bolus of fentanyl after the patch is applied. The patch releases fentanyl at a constant rate until the reservoir is depleted. Alcohol (0.1 mL/10 cm²) is used in the patch to increase the permeability of the skin to fentanyl. Only trace amounts of alcohol are absorbed systemically. On initial application of the patch, a subcutaneous “depot” is formed as fentanyl saturates the subcutaneous fat beneath the patch. After approximately 12 hours, steady-state plasma fentanyl concentrations are reached, which are then maintained for about 72 hours. Fentanyl patches currently are available in 12.5-, 25-, 50-, 75-, and 100-mcg/hour dosages. Multiple patches may be placed if higher doses are needed. The bioavailability of transdermal fentanyl has been calculated in one study to be approximately 90 percent (Varvel 1989). Transdermal fentanyl is now an indispensable tool in the management of cancer pain and chronic nonmalignant pain.

Patient-controlled transdermal fentanyl

The fentanyl hydrochloride patient-controlled transdermal system (PCTS) is a self-contained, needle-free, credit card-sized fentanyl delivery system. PCTS devices are worn on the arm or chest and use iontophoretic technology to deliver preprogrammed doses of fentanyl into the systemic circulation when activated by the patient on demand. PCTS is as safe and effective as IV morphine and PCA, and it is superior to placebo for managing acute postoperative pain. Passive absorption of the drug from PCTS is clinically insignificant when the device is not activated. In contrast, the transdermal fentanyl patch delivers fentanyl continuously for 72 hours via passive absorption and creates a subcutaneous depot of fentanyl, allowing for continued absorption of the drug even after the patch is removed, which results in a longer duration of action than with the IV formulation of fentanyl. Serum concentrations of fentanyl administered by PCTS decline rapidly after it is removed from the skin in a manner similar to the decrease in serum fentanyl concentrations following the cessation of IV fentanyl treatment. The duration of action of PCTS is similar to that of the IV formulation of fentanyl; thus, the depot effect is negligible. PCTS allows patients to control the amount of analgesic they receive; no such control is afforded by the passive transdermal fentanyl patch. Therefore, the patch is better suited for the management of chronic pain, whereas PCTS is more appropriate for acute pain.

Buprenorphine transdermal delivery

Buprenorphine is a low-molecular-weight, lipophilic, opioid analgesic that is being tested in transdermal matrix patch formulations for delayed release over a 72-hour period. Several clinical trials have demonstrated satisfactory analgesia with transdermal buprenorphine, with minimal requirement for rescue medication in patients with chronic cancer and noncancer pain (Sorge 2004). Further, despite the availability of rescue medication to all patients, those receiving transdermal buprenorphine tended to experience greater pain relief, reduced pain intensity, and longer pain-free sleep. Transdermal buprenorphine was generally well tolerated. Systemic adverse events were typical of opioid treatment or were attributable to the underlying disease.

Transdermal opioids are contraindicated for use in acute postoperative pain or in opioid-naïve patients because of the risk of serious adverse events, such as respiratory depression. Transdermal fentanyl has a slow onset of action and the side effects of respiratory depression and sedation may not be quickly reversible. Also, vigorous exercise and elevation of body temperature (due to fever, warm bath, heating pads, etc.) will increase blood flow to the skin, thereby increasing drug diffusion into the systemic circulation (Sebel 1987). Thus, the transdermal fentanyl system is best suited for patients with stable pain in whom the 24-hour opioid requirement already has been determined.
Targeted peripheral analgesics

The use of topical preparations in the management of pain has the distinct advantage of delivering analgesic medications directly to the painful area. Unlike the previously described transdermal delivery systems, systemic absorption of topical medications is minimal. Limited systemic absorption has the advantage of fewer drug-drug interactions and systemic toxicity or serious adverse events.

The topical agents approved for use as analgesics include topical capsaicin cream and lidocaine. Capsaicin binds to peripheral nociceptive terminals containing the neurotransmitter substance P. If able to tolerate the initial burning effects, a proportion of patients may experience analgesia related to the depletion in peripheral substance P. Topical lidocaine is available as a cream (EMLA [eutectic mixture of local anesthetics] cream: lidocaine 2.5 percent and prilocaine 2.5 percent) and a topical lidocaine (5 percent) patch. Unlike the cream formulation, no significant changes in dermal sensitivity occur with the patch formulation. Due to the need for repeated administration, patient compliance with topical creams may be difficult.

The topical lidocaine 5 percent patch is FDA approved for treatment of postherpetic neuralgia (PHN), traditional treatments for which have included tricyclic antidepressants, anticonvulsants, and opioids. Adverse systemic effects associated with these agents led to the development of a targeted peripheral analgesic. Because of its positive efficacy-and-safety profile (Davies 2004), the lidocaine 5 percent patch has been recommended as a first-line therapy for the treatment of the neuropathic pain of PHN (Dworkin 2003). It also has also been successfully utilized in the treatment of osteoarthritis, low back pain, neuropathy, and other neuropathic pain syndromes.

Most clinicians recognize the benefit of polypharmacy in pain management, and therefore, commonly use topical agents in combination with systemic analgesics when necessary. Although targeted peripheral analgesics may have a more favorable side-effect profile when compared to certain systemic analgesics, it is important to note that the indications for their use also may differ significantly. Prior to initiating any therapy, clinicians must ensure that patient selection and other clinical criteria are thoroughly evaluated.

OTHER ADMINISTRATION ROUTES

In addition to the delivery systems described above, analgesics have been given in extreme circumstances via the intra-arterial route, intraperitoneal route, pulmonary route, and cutaneous (conjunctiva, nasopharynx, vagina, colon, urethra, and urinary bladder) routes. These administration techniques are not commonly used, and their use necessitates the skill of an experienced clinician.

CONCLUSION

Several factors must be considered to determine the most effective, cost-effective, and user-friendly delivery system to manage chronic pain. Some of these factors are the ability of the patient to use a specific type of delivery system, efficacy of that system to deliver acceptable analgesia, ease of use for the patient and family, complications associated with that system, and cost of the delivery system.

The oral route of delivery should be the first choice for patients with chronic pain. If the oral route cannot be used because of gastrointestinal obstruction and/or severe nausea/vomiting, the rectal route may be considered. With the oral and rectal routes, controlled-release preparations should be used around the clock, with immediate-release preparations available to treat breakthrough pain. For treatment of breakthrough pain in a patient unable to take oral or rectal medications, a transmucosal preparation of fentanyl may be appropriate. For noninvasive alternatives, the transdermal route should be considered. PCA can be given to those patients in whom oral, rectal, and transdermal analgesics are not appropriate. Subcutaneous PCA does not require IV access and is relatively easy to administer. Intravenous administration of opioids is an option for those patients in whom no other route is available and who have IV access. For those patients in whom oral and other parenteral routes have been effective but poorly tolerated, the neuraxial route may be appropriate. This route may be most successful when opioids and local anesthetics and/or clonidine are used in combination.

REFERENCES


Benefits of Pain Management In the Elderly

PERRY G. FINE, MD
University of Utah
National Hospice and Palliative Care Organization

SUMMARY

Pain management for older adults necessitates a careful balancing of benefit and risk. Nonopioids and opioids to treat chronic and severe pain represent drug choices that, when properly managed in accordance with accepted clinical practice guidelines, can improve quality of life. This article reviews the pharmacotherapeutic options available for treating pain in the elderly.

Many older adults assume that pain is a natural part of aging and may not tell their doctors about it. Unaddressed pain, however, can greatly diminish independence and interfere with a patient’s quality of life, especially when it is persistent or severe. Aside from the subjective nature of suffering, both chronic and acute pain compromise immune competency, functional capacities, and cognitive and mood states. Simply put, failure to adequately treat pain increases morbidity and leads to increased health care utilization (Fine 2004).

Adequate pain control often necessitates the use of pharmaceuticals, and a range of pain-relieving drugs and delivery systems is available. In general, pharmacotherapy in older patients necessitates a delicate and cautious balancing of benefits weighed against risks. To achieve this balance, the physician needs to consider a host of factors that generally do not apply to younger patients, as they may not have the multiple chronic conditions and the organ system changes associated with aging that influence response to drug therapy. All coexisting conditions, as well as medication- and pain-related issues, should be fully apparent to the treating physician when determining which pharmacotherapeutic approach would be safest and most effective for an elderly patient.

As people age, they become more sensitive to the therapeutic effects and adverse reactions of pain medications (Rooke 2002). Indeed, most biological changes associated with aging alter how the body processes pain-relieving drugs (pharmacokinetics), as well as responds to these drugs (pharmacodynamics) (Table 1). Chronic medical conditions associated with advancing age, such as coronary artery disease, diabetes, and dementia, further influence pain management pharmacotherapy (Table 2).

If a patient is taking multiple prescription drugs, there are also issues of drug-drug interactions to consider. The same is true for certain dietary supplements, herbal
remedies, nutraceuticals (nutrient-enriched processed foods), and over-the-counter drugs that many elderly people take with or without their physician’s knowledge. In short, when treating elderly people for pain, consideration of drug-drug and disease-drug interactions are the rule rather than the exception.

As in younger populations, people who are 70 and older experience a broad range of responses to pain-control medications. The variability of drug responses observed more likely results from “tightly controlled but individually different cell- and tissue-specific patterns of gene expression,” rather than age-specific genetic instability (Arking 2001). Each patient has a unique pattern of organ function (or dysfunction) and subjective responses to therapy stemming from his or her medical history, environmental factors, and genetic makeup (Barja 1998). Sensitivity to drugs that act on the central nervous system, best demonstrated in studies of opioid analgesics, also increases with age (Rooke 2002).

Literature reviews reveal a dearth of well-controlled outcome studies specific to older patients with persistent pain. The lack of data complicates matters for physicians seeking guidance or algorithms for treating chronic pain syndromes in their patients. With few exceptions, results of studies of younger populations need to be adapted to older populations, and consensus views must substitute for empirically derived data.

In the few studies that have evaluated how opioid analgesics affect older patients, it was found that the rate of drug delivery — not the absolute dose of drug over time — influenced both the positive and adverse effects, including the most feared risk of life-threatening respiratory depression (Aubrun 2002). These studies support titration protocols that start with the lowest anticipated effective dose of the indicated drug and establish a monitoring and titration schedule. This schedule should be based on expected absorption, known pharmacokinetics, likely drug interactions, and side effects.

**PRINCIPLES OF PHARMACOTHERAPY IN OLDER PATIENTS**

The American Geriatric Society (AGS) has issued evidence-based general and specific guidelines for treating persistent pain in older patients (Table 3, page 48).

As noted in the AGS’s updated clinical guideline, *Management of Persistent Pain in Older Persons,* "Pharmacotherapy continues to be the mainstay of treatment to control pain in older patients" (AGS Panel 2002). This statement stems from the preponderance of evidence indicating a high prevalence of pain in the geriatric population. The incidence and severity of pain shown to exist in a significant percentage of older adults interfere with activities of daily living, quality of life, sleep, mobility, mood, and cognitive functioning (Helme 1997). Evidence also shows that all drug therapies potentially have negative side effects and that it is unrealistic to assume that any one treatment will provide complete pain relief. With enough knowledge and experience in the art and science of pharmacological pain management, however, it is reasonable to expect that serious pain can be significantly decreased in the majority of cases. The prescribing physician must be aware of the potential risks associated with analgesic and pain-modulating therapies and should establish a monitoring schedule tailored to the clinical and social circumstances of each patient with persistent pain. At the same time, the physician should not allow fears of potential side effects to override the need

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Age-related changes affecting pharmacokinetics and pharmacodynamics</th>
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<tbody>
<tr>
<td>Body composition (fat increases, lean body mass decreases, changing distribution of drugs)</td>
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<tr>
<td>Gastrointestinal motility (decreases, leading to longer transit times)</td>
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<tr>
<td>Cardiac output (decreases, leading to longer circulation, uptake, distribution times)</td>
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<tr>
<td>Renal clearance (decreases, leading to drug or drug metabolite accumulation)</td>
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<td>Protein binding (decreases, leading to more available drug)</td>
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<td>Nervous system senescence (decreased resilience, increased drug effects)</td>
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<tr>
<th>TABLE 2</th>
<th>Common chronic conditions of aging that affect drug disposition and lead to drug-drug and drug-disease interactions</th>
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<tbody>
<tr>
<td>Congestive heart failure</td>
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<tr>
<td>Coronary artery disease</td>
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<tr>
<td>Obstructive airways disease</td>
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<td>Peripheral arterial disease</td>
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<td>Hypertension</td>
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<td>Cerebrovascular disease</td>
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<td>Malignancy</td>
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<td>Arthritis</td>
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<tr>
<td>Diabetes</td>
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<td>Osteopenia, osteoporosis</td>
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<tr>
<td>Sensory impairments (vision, hearing)</td>
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<tr>
<td>Dementia (memory, judgment, communication, self-care)</td>
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<tr>
<td>Parkinsonism, neuralgias, balance disturbance</td>
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</table>
TABLE 3

Key recommendations for the management of persistent pain in older persons

- All older patients with functional impairment or diminished quality of life as a result of persistent pain are candidates for pharmacologic therapy.
- There is no role for placebos in the management of pain. Their use is unethical.
- The least toxic means of achieving pain relief should be used. When systemic medications are indicated, noninvasive routes should be considered first.
- Acetaminophen should be the drug of first consideration in the treatment of mild to moderate pain of musculoskeletal origin.
- Traditional nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided in patients who require long-term daily analgesic therapy. COX-2 selective agents or nonacetylated salicylates are preferred for older persons who require NSAIDs.
- Opioid analgesic drugs may help to relieve moderate to severe pain, especially nociceptive pain.
- Opioids for episodic (noncontinuous) pain should be prescribed as needed, rather than around the clock.
- Long-acting or sustained-release analgesic preparations should be used for continuous pain.
- Breakthrough pain should be identified and treated by the use of fast-onset, short-acting preparations.
- Constipation and opioid-related gastrointestinal symptoms should be prevented. Assessment of bowel function should be an initial and ongoing process during every follow-up visit for patients receiving analgesics.
- Nonopioid pain-modulating medications may be appropriate for some patients with neuropathic pain and some other chronic pain conditions.
- Patients taking analgesic medications should be monitored closely.
  - Patients should be reevaluated frequently for drug efficacy and side effects during initiation, titration, or any change in dose of analgesic medications.
  - Patients should be reevaluated regularly for drug efficacy and side effects throughout long-term analgesic drug maintenance.
  - Patients on long-term opioid therapy should be evaluated periodically for inappropriate or dangerous drug-use patterns.
- Clinical endpoints should be decreased pain, increased function, and improvements in mood and sleep — not decreased drug dose.

SOURCE: AGS 2002

for palliative pharmacotherapy, considering the life-altering nature of persistent pain.

Effectiveness and cost considerations

Slow, careful titration of drugs with specific subjective and objective endpoints is one of the keys to success in the application of pharmacotherapy in geriatric pain management. Another is to anticipate, prevent, and treat adverse effects, such as constipation, sedation, ataxia (dysmobility and falls), nausea, and cognitive disturbances, including delirium. A more rapid titration of pain drugs is necessary to control symptoms in patients suffering from severe acute pain and highly debilitating persistent pain. Some of these patients may need to be hospitalized for diagnosis, aggressive treatment, and close monitoring of the treatment’s safety and efficacy (Grossberg 2000, Fine 2001).

Dosing schedules for drug therapies also help to determine overall effectiveness. As with other chronic conditions, including hypertension and high cholesterol, medications for continuous pain are best given on a time-contingent basis (Max 1999). Sometimes, a patient needs supplemental doses of an immediate-release, short-acting analgesic prior to engaging in activities known to exacerbate pain. Chronic, unrelieved pain is an exhausting experience, as it commonly leads to sleep deprivation, poor nutrition, and deconditioning.

Drug regimens for elderly patients should be simplified as much as possible and adjusted to meet each individual’s needs and lifestyle (Fine 2000). Most patients will cope better if their pain drugs are prescribed to support exercise, enjoyable activities, and restorative sleep (AGS Panel 1998). Patients with primary insomnia as well as chronic pain require therapy aimed at mitigating both disorders, as each exacerbates the other. Sleep deprivation is so common in chronic pain that many patients seem to sleep continuously for a few days after their pain is finally relieved. This kind of restorative sleep is considered healthy, as long as the patient can be easily awakened to eat, drink, and use the bathroom. Once the patient is rested, the drug dose should be reduced if the sedation effect does not disappear in a few days (Fine 2001).

Physicians also should consider the cost of pain drugs, once sound principles of assessment and treatment have been followed. Low-income and indigent elderly patients, if they enrolled in advance, can obtain partial or complete coverage for selected pain management drugs under Medicare Part D, effective Jan. 1, 2006. There is some speculation that moderate-income Medicare beneficiaries, however, may not purchase Part D coverage in large numbers because of its associated out-of-pocket costs. In addition to any lack of reimbursement from Medicare or a private insurance plan, other barriers clini-
nicians should consider are limited formularies and po-
tential delays by mail order pharmacies under managed
care programs. Inner-city areas may not have pharmacies
willing to carry certain opioid analgesics (Morrison 2000).

Clinicians also should consider each pain drug’s phar-
camokinetic profile as well as relevant patient vari-
ables, such as kidney and liver function and concurrent
medication use. Armed with this knowledge, the clinician
can establish a titration schedule based on anticipated at-
tainment of steady-state blood levels with consequent ef-
ffects. For healthy patients taking short half-life drugs, this
process may take 1 to 2 days. Several days to a week may
be needed for drugs that have long half-lives or when
 treating patients with diminished hepatic metabolism,
impaired renal clearance, cognitive deficits, or unreliable
social settings (Grossberg 2000, Raffa 2001).

Pharmacotherapy usually is started after nonphar-
caceutical therapies, such as distraction (e.g., music) and
other modalities (e.g., transcutaneous electrical nerve
stimulation [TENS]) have failed. Pain relief is maxi-
imized when pharmacological and nonpharmacological
treatments are used in concert (AGS Panel 1998, Ferrell
1996, Gloth 2001). Combining drugs with different
mechanisms of action may lead to improved outcomes
owing to therapeutic synergy, with less toxicity than can
occur when higher doses of single drugs are used (Raffa

This approach has been termed “rational polyphar-
macy,” and its practice principle has been best dem-
strated in a study by Gilron (2005). In this randomized,
double-blind study, morphine alone, gabapentin alone,
and a combination of the two were evaluated in the treat-
ment of 41 patients who completed the trial and who had
either postherpetic neuralgia or diabetic neuropathy and
a mean age 68 and 60, respectively. Gabapentin plus
sustained-release morphine, at lower doses of each drug
than were used in the single drug groups, led to lower
pain ratings than were seen in those groups treated with
morphine alone (P<.04), gabapentin alone (P<.001), or
placebo (P<.001). Common side effects included con-
stipation, sedation, and dry mouth. Not surprisingly,
the combination therapy group also had improved qual-
ity-of-life outcome scores.

Occasional and specific indications for injection ther-
apies, nerve blocks, and other interventional therapies in
the management of chronic pain also apply (Weiner
2002). In the majority of cases, however, noninvasive
drug delivery represents the most common and readily
available means of obtaining symptomatic relief and op-
timal functioning over the long term.

In some cases, a specific disease-modifying drug is in-
dicated (e.g., for rheumatoid arthritis or ischemic heart
disease), or a drug class with a specific mechanism of ac-
tion is needed (e.g., anti-inflammatory or osteoclast in-
hibition). For most mild to moderate persistent pain
syndromes, absent such clear pathophysiological ther-
apeutic indications, clinicians should start with a rela-
tively weak nonopioid analgesic, such as acetaminophen.
If that fails to adequately treat the pain, a more potent
analgesic anti-inflammatory drug or a neurotransmitter-
modulating and membrane-stabilizing drug, such as an
anticonvulsant or antidepressant, is indicated. For more
severe pain, the next step in the progression of drug ther-
apies would be an opioid (Tables 4a and 4b, pages 50 and
51). Unless pain is severe, it seems reasonable to start with
a drug having the lowest risk of toxicity (Leipzig 1999).

APPLIED PHARMACOTHERAPY:
NONOPIOIDS

Patients with mild to moderate musculoskeletal pain
may obtain sufficient symptomatic relief with round-the-
clock doses of acetaminophen — a simple and inexpen-
sive approach. For patients with normal renal and hepatic
function without a history of alcohol abuse, the maxi-

mum recommended dose is 4,000 mg per day. If the pa-

tient has hepatic or renal impairment, the acetamin-
ophen dose should be reduced by 50 percent to 75
percent, or an alternative form of therapy should be used
(Simon 2002). Chronic use of nonselective nonsteroidal
anit-inflammatory drugs (NSAIDs) by older patients,
especially those with a multiple-system disease and the
very frail, carries a high risk for life-threatening gastro-
intestinal bleeding (MacLean 2001, Silverstein 2000). Al-
though simultaneous administration of misoprostol or
proton pump inhibitors has been shown to reduce this
risk, these pharmacological additions are often not well
tolerated by elderly people (Graham 1993).

When acetaminophen is ineffective, potentially safer
alternatives to NSAID therapy for patients who require
daily therapy for chronic pain are the COX-2 selective
agents (Simon 2002). Celecoxib, a sulfonamide, is the
only oral drug available, now that rofecoxib and valde-
coxib have been removed from the market because of
concerns about cardiovascular and cerebrovascular risks.

The COX-2 selective drugs are less likely than the non-
selective NSAIDs to cause gastrointestinal bleeding dur-
ing the first weeks to months of use. Because the COX-2
inhibitors are still relatively new, clinicians must monitor
closely for drug–drug and drug–disease interactions, and
stay abreast of postmarketing reports, advisories, and re-
views. In many cases, it appears that ongoing low-dose
opioid therapy for a wide variety of chronic pain syn-
dromes actually may pose fewer life-threatening risks
than does the long-term daily use of high-dose NSAIDs

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## Selected oral drugs for the treatment of persistent pain

### NONOPIOIDS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Usual effective dose (maximum dose)</th>
<th>Titration</th>
<th>Notes</th>
</tr>
</thead>
</table>
| Acetaminophen (Tylenol) | 325–500 mg every 4–6 hours | 2,000–4,000 mg/24 hours (4,000 mg/24 hours) | After 4–6 doses | ‣ 4,000 mg/24 hours  
‣ Reduce maximum dose 50%–75% in patients with history of alcohol abuse |
| Celecoxib (Celebrex)   | 100 mg daily to 2×/day | 200 mg/24 hours (400 mg/24 hours) | After 2–3 days     | ‣ Higher doses (400 mg/24 hours) associated with higher incidence of GI or CV side effects  
‣ Patients with indications for cardioprotective ASA require aspirin supplement |
| Corticosteroids (prednisone) | 2.5–5.0 mg daily | Variable | After 2–3 doses | ‣ Use lowest possible dose to prevent chronic steroid effects  
‣ Anticipate fluid retention and glycemic effects |
| Tricyclic antidepressants (desipramine [Norpramin], nortriptyline [Aventyl, Pamelor]) | 10 mg HS | 25–100 mg HS (Variable) | After 3–5 days | ‣ Significant risk of adverse effects in older patients  
‣ Anticholinergic effects |
| Anticonvulsants        |               |                                     |                     |                                                                      |
| -Carbamazepine (Tegretol) | 100 mg daily | 100–800 mg 3×/day | After 3–5 days | ‣ Monitor LFTs, CBC, BUN/serum creatinine |
| -Clonazepam (Klonopin) | 0.25–0.5 mg HS | 0.5–1.0 mg daily 2×/day | After 3–5 days | ‣ Monitor sedation, memory, CBC |
| -Gabapentin (Neurontin) | 100 mg HS | 300–900 mg 3×/day (3,600 mg) | After 1–2 days | ‣ Monitor sedation, ataxia, edema |
| Mexiletine (Mexitil)   | 150 mg | 150 mg 3×–4×/day (Variable) | After 3–5 days | ‣ Avoid use in patients with conduction block, bradyarrhythmia; monitor EKG |
| Baclofen (Lioresal)    | 5 mg | 5–20 mg 2×–3×/day (Highly variable) | After 3–5 days | ‣ Monitor muscle weakness, urinary function  
‣ Avoid abrupt discontinuation due to CNS irritability |

### SNRI antidepressant

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Usual effective dose (maximum dose)</th>
<th>Titration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duloxetine (Cymbalta)</td>
<td>20 mg daily</td>
<td>Starting dose up to 60 mg daily</td>
<td>As tolerated</td>
<td>‣ Monitor sedation, nausea, ataxia</td>
</tr>
</tbody>
</table>
### Selected oral drugs for the treatment of persistent pain (continued)

#### OPIOIDS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose</th>
<th>Usual effective dose (maximum dose)</th>
<th>Titration</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol (Ultram)</td>
<td>25 mg every 4–6 hours</td>
<td>50–100 mg (300 mg/24 hours)</td>
<td>After 4–6 doses</td>
<td>• Mixed opioid and central neurotransmitter mechanism of action; proprietary combination of tramadol 37.5 mg/acetaminophen 325 mg is available</td>
</tr>
</tbody>
</table>
| Hydrocodone (e.g., Lorcet,* Lortab,* Vicodin,* Vicoprofen)† | 5 mg every 4–6 hours, as needed | 5–10 mg (max: see notes)          | After 3–4 doses | • Useful for acute recurrent, episodic, or breakthrough pains  
  • Daily dose limited by fixed-dose combinations with acetaminophen or NSAIDs |
| Oxycodone IR (OxyIR)  | 5 mg every 4–6 hours, as needed | 5–10 mg (max: see notes)          | After 3–4 doses | • Useful for acute recurrent, episodic, or breakthrough pains  
  • Daily dose limited by fixed-dose combinations with acetaminophen or NSAIDs |
| Oxycodone SR (OxyContin) | 10 mg every 12 hours | Variable                           | After 3–5 days | • Usually started after initial dose is determined by effects of immediate-release opioid  
  • May require dosing every 8 hours |
| Morphine IR           | 2.5–10 mg every 4 hours | Variable                           | After 1–2 doses | • Oral liquid concentrate recommended for breakthrough pain |
| Morphine SR           | 15 mg every 12 hours | Variable                           | After 3–5 days | • Usually started after initial dose is determined by effects of immediate-release opioid  
  • Toxic metabolites of morphine may limit usefulness in patients with renal insufficiency or when high-dose therapy is required  
  • 12- and 24-hour CR formulations may require more frequent dosing if EOD failure occurs regularly |
| Hydromorphone (Dilaudid) | 2 mg every 3–4 hours | Variable                           | After 3–4 doses | • An alternative to SR opioid formulations for breakthrough pain or for around-the-clock dosing |
| Transdermal fentanyl (Duragesic) | 12 mcg patch every 72 hours³ | Variable                           | After 2–3 patch changes | • Usually started after initial dose is determined by effects of immediate-release opioid  
  • Lowest-dose patch (12 mcg/hour) recommended for patients who require 30–60 mg/24 hours of oral morphine equivalents  
  • Peak effects of first dose usually take 18–24 hours  
  • Duration of effect usually 3 days but may range from 48–96 hours |

ASA=acetylsalicylic acid, BUN=blood urea nitrogen, CBC=complete blood count, CNS=central nervous system, CR=controlled release, EKG=electrocardiogram, EOD=end-of-dose, GI=gastrointestinal, HS=at bedtime, IR=immediate release, LFT=liver-function test, SNRI=serotonin and norepinephrine reuptake inhibitors, SR=sustained release.

*Hydrocodone plus acetaminophen.
†Hydrocodone plus ibuprofen.
‡Updated from original AGS guideline.
SOURCE: ADAPTED FROM AGS 2002
Neuropathic pain (pain generated by injury to or diseases of the nervous system) is extremely difficult to treat. Traditional teaching is that opioid analgesics are ineffective against neuropathic pain (Arnér 1988). This attitude has changed recently owing to findings of controlled clinical trials, as well as mounting clinical experience (Rowbotham 1999). These findings are extremely important for elderly patients, who have an increased susceptibility to developing neuropathic pain syndromes, such as postherpetic neuralgia, a complication of herpes zoster, commonly known as shingles (Watson 1998). Nevertheless, typical analgesics alone rarely provide adequate relief from the severe and debilitating persistent pain that can arise from such neurological conditions as herpes zoster, diabetic neuropathy, poststroke central pain, and phantom limb pain (Bennett 1999).

The tricyclic antidepressants (TCAs) have shown positive outcomes in neuropathic pain studies, that have led to wider use of this class of drug to treat neuropathic pain (McQuay 1996, Sindrup 1999). Unfortunately, these drugs have anticholinergic effects that lead to dry mouth, sedation, and other nuisance side effects, as well as morbidity effects like ataxia, memory impairment, and arrhythmias. Use of TCAs therefore is discouraged. In selected cases, however, extremely low doses of the lesser anticholinergic agents (e.g., nortriptyline, desipramine) under careful observation and very slow titration may be appropriate (Lipman 1996). Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, and sertraline, have not been shown to be effective for neuropathic pain. Combined serotonin and norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine or duloxetine, do show efficacy, and duloxetine was approved in 2004 for painful diabetic neuropathy (Dworkin 2003a, Barkin 2005).

Drugs developed and approved for seizure disorders are thought to reduce neuropathic pain by altering sodium channel and voltage-gated calcium channel conductance. These newer drugs, which are safer and less toxic than TCAs, nonetheless carry higher price tags. Clinical trials are under way for some of these medications, including oxcarbazepine, tiagabine, topiramate, lamotrigine, and gabapentin. So far, only gabapentin has been proven effective in methodologically sound clinical trials (Dworkin 2003b) and has been approved for postherpetic neuralgia.

In some cases, effective pain control can be achieved with topical agents, such as capsaicin and lidocaine (Barbano 2004). The 5 percent lidocaine patch is among the agents recommended as a first-line therapy for the treatment of neuropathic pain, in guidelines developed by the

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Fourth International Conference on the Mechanisms and Treatment of Neuropathic Pain (Dworkin 2003a). Specifically indicated for postherpetic neuralgia, the 5 percent lidocaine patch provides a nonsystemic alternative to gabapentin or antidepressants (see Argoff article in this publication, page 24).

### Applied Pharmacotherapy: Opioids

Opioid analgesics for treating chronic noncancer pain has become more acceptable over the past 10 years, due largely to observations of benefit derived from long-term opioid use in cancer patients (Max 1999, Portenoy 1994). A number of different opioid analgesics and formulations are available (Tables 4a and 4b, pages 50 and 51). In selecting an opioid analgesic for an elderly patient, several factors should be considered (Hanks 1998):

- Pattern and intensity of the patient’s pain
- Previous responses to opioid therapy
- Adherence to dosing regimens
- Routes of administration
- Convenience for the patient and caregiver
- Cost

The mixed agonist-antagonist agents (e.g., pentazocine) are contraindicated due to excessive risk of cognitive disturbances and adverse interactions with other opioids (Lipman 2002). One of the most extensively prescribed analgesics in older patients is propoxyphene, which has been on the market for decades (Cramer 1994). In selecting an opioid analgesic for an elderly patient, several factors should be considered (Hanks 1998):

- Cost
- Routes of administration
- Convenience for the patient and caregiver
- Previous responses to opioid therapy
- Adherence to dosing regimens
- Pattern and intensity of the patient’s pain

The analgesic tramadol has a dual mechanism of action, with both opioid and monoamine neurotransmitter-mediated effects. Opioid agonist effects directly inhibit nociception, and inhibition of norepinephrine and serotonin reuptake enhance endogenous descending pain-inhibitory pathways. These mechanisms are thought to reduce ascending nociceptive signals, and thus mitigate the perception of pain. Tramadol has been shown to be effective in treating mild to moderate pain in osteoarthritis, low back pain, and diabetic neuropathy.3 In a recent review of tramadol use in older patients, its effectiveness and safety were similar to equal doses of opi-
Opioid analgesics, such as hydrocodone and codeine, and showed a lower incidence of constipation (Schnitzer 2000a). Tramadol combined with acetaminophen results in quicker and more potent pain relief. A fixed-dose combination is now available to treat acute and recurrent pain episodes (Gloth 2001). Tramadol has a relatively low diversion and abuse rate compared with other opioids (Cicero 1999).

Use of methadone, a potent mu opioid agonist, for pain control has gone in and out of fashion through the years. Pain specialists have recently renewed their interest in this agent because it is thought to be effective for neuropathic pain due to weak affinity and antagonism at the N-methyl-d-aspartate (NMDA) receptor site. Methadone also may retard the development of opioid tolerance (Ayonrinde 2000, Bruera 2002). Methadone, however, has a long and highly variable half-life, which makes it difficult to titrate, posing a problem for older patients because adverse effects from drug accumulation may arise days after regular dosing. Any clinician with a U.S. Drug Enforcement Agency license for Schedule II controlled substances is authorized to prescribe methadone for pain indications, but the drug should be used under the direction of a physician who has considerable experience and where a responsible caregiver can monitor potential adverse effects.

In monitoring the side effects of opioid therapy, physicians should focus primarily on neurologic, gastrointestinal, and cognitive-behavioral problems. These include gait disturbance (ataxia), dizziness, falls, itchiness, constipation, abdominal bloating or discomfort, nausea, sedation, impaired concentration, and delirium (Weiner 2002, Derby 1997, Walsh 1990). For older patients who have a driver’s license, it makes sense to restrict driving until maintenance dosing has been established and until the extent of cognitive impairment is determined (Leipzig 1999). Serious side effects — such as muscle spasms (myoclonus), impaired consciousness or delirium, and life-threatening respiratory depression (hypoxia) — are rare, especially when dosing starts low and is escalated slowly, allowing for blood levels to stabilize at each dose prescribed (Grossberg 2000).

Patients with limited mobility and a propensity for falls must be monitored carefully for aggravated gait and balance problems (Weiner 2002). These patients may need to be evaluated during the titration phase for an assistive device or physical therapy. For continuous treatment of moderate to severe pain, sustained-release opioid formulations are available (Fleischmann 2001, Caldwell 1999, Ahmedzai 1997). Currently, controlled-release morphine and oxycodone, as well as transdermal fentanyl, are available in a wide range of strengths. To prevent accidental and potentially fatal overdose, physicians should inform patients and caregivers that chewing or crushing continuous-release tablets destroys their controlled-release properties, leading to rapid absorption of the entire dose.

Some degree of physical dependence is an inescapable reality of daily opioid use. Signs and symptoms of withdrawal characterize this predictable phenomenon if the drug is discontinued abruptly or an opioid antagonist is administered. If opioid use is no longer necessary, the symptoms of physical dependency can be avoided effectively by reducing the dose gradually over the course of 10 days to several weeks (Hare 1990). True addiction is a complex multifactorial pathological disorder unrelated to pain treatment; its hallmarks include craving and continued use regardless of ill effects (APS 2001).

Evidence from long-term studies of patients with stable disease suggests that opioid tolerance — the need for more drug to get the same therapeutic effect — is slow to develop (Fleischmann 2001, Lipman 2002, Harati 2000). If a patient requests a dramatic change in dosage, that should prompt an evaluation of disease progression.

As suggested previously, the imperative to assess and treat debilitating pain should supersede phobic concerns over opioid use (Portenoy 1996). Decisions regarding appropriateness or contraindications for opioid therapy should come only after a considered determination of benefits and risks, similar to all other long-term treatment plans that have significant clinical implications. To help educate health care professionals and improve access to appropriate therapeutics, state and federal agencies have issued prescribing guidelines, or have created new policies or reformed ineffective ones to support medically indicated use of opioid analgesics for patients with pain conditions (FSMB 1998).

### TREATING ACUTE PAIN

The principles of treating acute pain in older patients are similar to those used for long-term pain management, but there is usually a discrete time period involved, coincident with the cause of pain. Typically, trauma and surgery are the primary indications for anti-inflammatory and opioid analgesics in older patients. These patients commonly experience acute episodic disorders, such as acute gouty arthropathy, nephrolithiasis, and acute herpes zoster, which may warrant both disease-modifying and palliative analgesic therapies. If pain is so debilitating that hospitalization is warranted, use of therapies such as patient-controlled analgesia (PCA) or regional anesthesia/analgesia techniques (e.g., continuous epidural) may be indicated. It must be remembered that acute pain in older patients warrants rapid evaluation and treatment to prevent stress-induced cardiac (or other) morbidity. Adverse effects associated with anal-
Elderly Patients

...gescic agents are the same when they are used for acute pain as they are for chronic pain, with the chief consideration being the dose and rate of titration. For acute pain that is out of control, more rapid dose escalation may be indicated and would warrant closer clinical monitoring.

CONCLUSIONS

Adherence to clinical practice guidelines should serve to promote improved outcomes in patients who suffer from acute and persistent debilitating pain. Each patient’s experience and response to drug therapy will be unique; therefore, there is no substitute for continual, individualized assessment, determination of realistic goals, and monitoring of outcomes.

As clinicians gain more experience in treating chronic pain in older patients, the importance of having a variety of drug choices becomes increasingly evident. When building a nonparenteral formulary, a reasonable approach would be to include at least two drugs from each of the following classes and subgroups: opioids (oral and transdermal, long- and short-acting), selective and nonselective NSAIDs, TCAs, SNRIs, topical anesthetics (lidocaine 5 percent patch and EMLA cream), and anticonvulsants. Of the many different anticonvulsants, for example, only one or two may be effective in a given patient, or only one drug might be tolerable. Flexibility within the formulary is required, therefore, to account for such a range of responses within the population.

Given the tremendous intra- and interindividual variability in pain experiences and analgesic responses, every patient with chronic pain, in effect, becomes his or her own clinical trial. Health plan formularies that allow access to a broad range of pain medications provide physicians with the flexibility they need to tailor pain pharmacotherapy to each patient’s needs.

REFERENCES


White HS. Comparative anticonvulsant and mechanistic profile of the established and newer antiepileptic drugs. Epilepsia. 1999;40(suppl):S2–S10.
Chronic pain is a complicated disorder that is often caused by tissue damage. Yet such tissue damage occurs in the context of complex mental and social factors that influence and are influenced by pain. As the result of pain, patients often suffer significantly in areas that are above and beyond their pathophysiology — a loss of job or a failed relationship, for example. For these patients, a unidimensional approach to their condition rarely ameliorates their pain significantly.

Pain experts have argued that chronic pain sufferers require comprehensive care across multiple disciplines (Gatchel 1999). A multidisciplinary pain center therefore may offer the most timely, cost-effective, and efficient standard of care for these patients.

In the general medical environment, pain sufferers often must wait 3 months or more for referrals that allow them to see specialists in multiple clinical areas, while patients who enter a multidisciplinary pain clinic may see three, four, or even five specialists in a single day. For example, a patient may see a neurologist and then a psychiatrist in the morning, followed by a procedure that is performed by an anesthesiologist in the afternoon. Multidisciplinary care is complex, and clinics can spend years working out the nuances of smooth functioning to allow an ego-neutral, team-driven atmosphere to emerge; such efforts almost always result in improved patient outcomes.

For several reasons, MCOs have been slow to embrace the concept of multidisciplinary care, preferring to provide reimbursement for invasive techniques rather than referrals to multidisciplinary clinics (Hoffmann 1998). Some medical systems still are structured so that primary care physicians — as the gatekeepers of medical care — receive incentives for managing pain themselves and without providing a referral for specialty care, even when referrals are appropriate. This outdated and ineffective approach to health care delivery must be revisited to best serve a range of patient populations that includes patients with chronic pain.

FUNCTION OF MULTIDISCIPLINARY CLINICS

On a patient’s admittance to a multidisciplinary pain clinic, a triage nurse or similar professional will perform an initial evaluation of pain status and then refer the patient to the most appropriate clinician. The initial evaluation often will consist of a thorough physical assessment — a general physical examination, recording of...
vital signs, review of prior records, and other basic medical tests as indicated by the clinical condition. The goal of the evaluation is to assess the patient’s pain and validate the source of the pain, and determine which specialists the patient should see.

After the evaluation, the patient is routed in one of several directions, depending on the patient’s specific need. Each branch of multidisciplinary pain care — mental health, neurology, anesthesiology, nursing, social work, and occupational/physical therapy — plays a vital role in a patient’s overall well being and offers different services that may ameliorate or better manage a patient’s pain and concomitant physical and/or psychological disability.

Mental health
Most patients with chronic pain suffer from accompanying emotional disturbances such as depression, anxiety, self-denigration, anger, and hostility (Eccleston 2001). Increased emotional disturbance may be associated with diminished coping and increased reports of pain. The role of mental health professionals (psychologists and psychiatrists) at a multidisciplinary pain clinic is to treat or control these primary symptoms.

Psychologists, most often, are involved in the assessment and treatment of pain and psychiatric illness using psychotherapy, biofeedback, and relaxation training. Psychiatrists manage pain and pain-related affective disturbances by using medications. Psychologists and psychiatrists also may help patients redefine the pain-causing stimuli in more adaptive ways. This restructuring of thought can assist patients to better adjust to persistent pain. For example, rather than seeing themselves as completely disabled, patients are encouraged to define areas where they have competence and to tap into these strengths to make contributions to family, friends, or social institutions.

Individuals with chronic pain who are clinically depressed, experience difficulty adjusting to pain, are addicted to or psychologically dependent on prescription medications, or have a pre-existing mental disorder that may be exacerbated by chronic pain are among the most likely to benefit from psychological intervention (Campbell 2005). It is not uncommon for many pain patients to have more than one of these conditions concomitantly.

Neurology
Damage to the nervous system — including injuries to the brain, spinal cord, or peripheral nervous system — results in neuropathic pain. Infections, metabolic dysfunctions, and diseases also can produce neuropathy. Damage to the nervous system causes the brain to perceive damage to tissue even when it does not exist. In phantom limb pain, for example, the brain perceives tissue damage to an arm or leg when that limb is no longer present. Neurologists, using medications and mechanical devices (e.g., spinal cord stimulators) can significantly reduce, but rarely eliminate, neuropathic pain for many patients.

Anesthesiology
Anesthesiologists traditionally have been on the front line of pain treatment. Unlike the traditional role of administering sedation and analgesia that is assumed by many anesthesiologists in operating rooms, interventional anesthesiologists often use fluoroscopic injections, nerve blocks, intrathecal pump implantations, and other interventions to reduce and eliminate pain. They work closely with a team of professionals, including radiologists, nurses, and other technicians, to provide outpatient care when available or inpatient management when it is necessary.

Nursing
Nurses remain the hallmark of patient care. For many patients with pain, the nurse is a liaison between pain care and medical care, the lifeline to medication administration, and an empathetic listener. Skilled nurses often are essential to the early detection of affective disturbance (e.g., depression, anxiety) and changes in the patient’s disposition. In a multidisciplinary pain clinic, they assist in reducing suffering and provide technical assistance with many procedures (McCleary 2004).

Social work
Chronic pain also affects a patient’s family, and social workers generally are at the forefront of reducing family suffering by connecting them with resources that can improve their ability to manage the situation. Spouses, children, coworkers, and other everyday contacts frequently are affected as much, if not more, than the individual seeking pain treatment; this is attributable to the effects of reduced physical or emotional contact and can be a result of other relationship strains that are secondary to affective disturbance.

Chronic pain may cause psychosocial problems. As families fall apart and dynamics change, verbal and physical disputes can be natural extensions. When the primary wage earner is the patient with pain, financial problems may accumulate and challenge insurance coverage and consistency of care. Social workers are skilled in addressing many of these issues.

Physical/occupational therapy
Chronic pain sufferers often become kinesophobic — fearful of recreating any action that causes them pain.
These conditions sometimes are treated by psychologists, but physical and occupational therapists are much better equipped to evaluate physical activity levels, establish guidelines for daily activities, and execute a plan of increased physical activity aimed at reducing pain and improving physical conditioning. This behavioral inhibition can lead to serious and irreversible long-term physical problems, particularly atrophy and deconditioning. The initial phases of kinesophobia treatment may be plagued by increased pain, which then may bring about the need for support (e.g., coping skills training, temporary dosage increase in breakthrough medications) from all members of the treatment team.

**DIVERSITY IN CARE**

Tertiary multidisciplinary pain center staff also are adept at caring for a diverse patient population, which localized or single-focused pain care centers may not necessarily be staffed to handle. The more diverse the health care practitioners who interact with patients, the better the chances of forming a successful and comprehensive treatment plan for the patient.

Factors such as race, formal education, age, and geographical region may shape the way patients describe their pain. For example, patients with little formal education may not have the verbal skills to articulate the nature of their pain. Also, some populations find it difficult to convert their experience of pain into a 0-to-10 scale, a standard metric for the assessment of pain. Other populations, such as African-Americans and women, may be more likely to catastrophize their pain compared with their white or male counterparts.

A proficient multidisciplinary clinic with a diverse staff and patient base recognizes, appreciates, and integrates diversity into the assessment and treatment of the patient with pain, and can respond to all the factors that contribute to the experience of pain.

**IDENTIFYING THE RIGHT PATIENTS**

Patients with complicated pain — pain that is not resolved in a primary care physician’s office or by a single specialist — cannot be broadly dismissed as “faking” or seeking medication, two common characteristics of this population. Instead, clinicians should view these cases as providing an opportunity to conduct a more thorough assessment and to gather a team of professionals who will work toward reducing pain and managing it better. Clinicians should be aware of the full range of factors that may influence a patient’s pain experience, so that if they are faced with a patient whose pain issues cannot be resolved, they can determine the need to refer the patient to a pain specialist or multidisciplinary pain center.

The 20 percent of patients who report pain but who do not have their symptoms resolved in the first or second course of treatment would benefit most from treatment at a multidisciplinary pain clinic. Without such care, these patients can be a significant drain on the health care system, owing to multiple failed treatments in pursuit of a cure. In offering concurrent care from several types of professionals (who can help patients stabilize their symptoms, improve their coping skills, and shift their mentality from “cure” to “management”), multidisciplinary pain clinics often deliver positive treatment outcomes in a more cost-effective manner than when patients move from individual specialist to individual specialist in search of pain relief.

Multidisciplinary care, however, may not be appropriate for every patient who experiences pain. For most patients, traditional and relatively inexpensive treatments can be effective. A patient who sprains his ankle, for instance, will often require a visit to the emergency department and a prescription for painkillers: 2 weeks later, the pain is gone and life’s routine resumes. More problematic are those patients who, after weeks, months, and even years, continue to have pain from a simple injury after tissue damage has healed. For these patients, multidisciplinary care may be their only chance at regaining a functional lifestyle.

Primary care physicians are becoming increasingly more skilled at managing chronic pain. The proliferation of continuing medical education programs and the availability of specialized training programs has given them a better understanding of the psychosocial issues that influence pain and the variety of management options at their disposal. If they are unable to resolve a patient’s pain after several weeks of care, however, they should consider a referral to a specialist or a multidisciplinary pain clinic. However, they should not use that referral as an excuse to distance themselves from the patient’s care. Multidisciplinary clinics should not be seen as a place where patients who need narcotic management or who require long-term care are deposited. Multidisciplinary clinics are best utilized as consultant services. After a comprehensive treatment plan has been identified and implemented, the primary care physician plays an important role in continuing the long-term management of the patient’s pain.

**REIMBURSEMENT ISSUES**

Many pain care specialists, particularly those specializing in mental health, have difficulty receiving third-

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Quality of Care

Party payment for physical health coverage. Psychologists treating patients with pain who do not have a comorbidity (e.g., depression) are rarely reimbursed for treatment, even though data have shown that early psychiatric intervention costs far less than the management and maintenance of a pharmacological program and/or surgical solution (Morley 1999, Malone 1988, Turner 1996). The benefits of services by a psychiatrist or psychologist that MCOs might finance over a 6- or 8-week period can last a patient’s lifetime.

MCOs must be flexible and adapt to the trends of multidisciplinary care. The old model of pain management, which saw providers treating either physical health symptoms or mental health symptoms without any crossover of care, has been demonstrated to be ineffective and is increasingly obsolete. Psychologists are seeing just as many patients with chronic pain as neurologists. This fusing of traditional roles toward more effective pain management must be met with equal effort and flexibility by MCOs.

Most MCOs cover some part of multidisciplinary pain care — usually nerve blocks or surgical interventions — but many will not cover psychotherapy or biofeedback for pain management. A 1997 study showed that 46 percent of selected Blue Cross Blue Shield Association plans did not cover any behavioral interventions, while an even greater share — 63 percent — explicitly did not cover biofeedback (Gatchel 1999). This coverage approach does not serve the public effectively, given the demonstrated efficacy of behavioral interventions. Because MCOs do not cover all elements of multidisciplinary care, poor or economically disadvantaged patients — who often would benefit most from multidisciplinary services — cannot afford the out-of-pocket expenses needed to take advantage of the full range of multidisciplinary care services.

A primary reason that MCOs traditionally have been hesitant about reimbursing pain treatment, and particularly multidisciplinary care, is fear of fraud — and to be certain, the legitimacy of those fears cannot be discounted. Several published reports have exposed fraudulent pain care specialists (not necessarily those affiliated with multidisciplinary clinics) (Allstate 2004). 4

Unquestionably, improperly educated or credentialed practitioners should not be paid for treating patients for pain. To not cover any multidisciplinary pain program because of fear of fraud, however, is overly cautious. MCOs may benefit from more extensive research into existing clinics and pay for services by those that have demonstrated the capacity to effectively manage pain in a multidisciplinary environment.

In the mid-1990s, the Commission of Accreditation of Rehabilitation Facilities, in collaboration with the American Pain Society, developed standards for the accreditation of multidisciplinary clinics. Accreditation is not mandated on documented outcomes data, however; it only confirms that a clinic uses a multidisciplinary approach to chronic pain management. Accreditation, therefore, should not be the only mechanism used to decide which multidisciplinary clinics should be covered for their spectrum of services.

There are several potentially effective ways to determine which multidisciplinary pain centers should be eligible for comprehensive reimbursement:

- Ascertain the number of formalized patient complaints leveled against a center
- Ask to see a center’s standard of care and evaluate its competency, perhaps comparing it with gold standards in the field
- Follow up with treated patients on their outcomes after multidisciplinary care

A clinic or provider has met the threshold for reimbursement after competence has been demonstrated and practitioners have been properly trained and have participated in continuing education. The initial investment in the cost of multidisciplinary care will yield long-term monetary savings to an MCO.

Conclusion

Multidisciplinary pain care began as a working experiment in the 1970s; as trenchant clinical data accumulated — illustrating the efficacy of such an approach to chronic pain management — the number of multidisciplinary pain clinics in the United States grew rapidly. In the 1980s, the multidisciplinary clinic was perceived as the undeniable future of pain care. At that time, many well-respected pain specialists latched onto multidisciplinary pain clinics, believing that by doing so, they were giving the diverse range of chronic pain sufferers the best chance of receiving ongoing assistance.

Financial constraints caused by third-party payment and coverage policies, however, have forced dozens of multidisciplinary clinics to close their doors in the past decade. Today, fewer than 30 multidisciplinary pain care centers operate in the United States. Because multidisciplinary pain clinics that rely on insurance payment as their primary source of financial support are finding it more difficult to survive, the majority now are affiliated with major research-based universities, such as Duke University, that have such alternate means of financial

support as research grants and donors. This is a distressing trend.

For many MCOs, pain management remains a mystery. Therefore, plan administrators must take a more active role in educating themselves on multidisciplinary pain services and consider coverage of services from centers that have proven success in resolving symptoms and improving the function of chronic pain sufferers. To do otherwise would represent a regression in the care of patients with chronic pain.

REFERENCES


Maruta T, Swanson DW, McHardy MJ. Three year follow-up of patients with chronic pain who were treated in a multidisciplinary pain management center. Pain. 1990;41:47–53.


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