CENTER FOR THE TREATMENT OF PAIN

Dear Colleague:

Patients with chronic pain deserve a better quality of life.
Through education, we can take great steps toward achieving this goal.

Over 75 million Americans experience chronic pain—more than those with diabetes, heart disease, and cancer combined. Pain is also **the most common reason for individuals to seek healthcare in the United States**. Despite advances in our understanding of pain and its treatments, a wide treatment gap remains: 1 in 4 patients with chronic pain has changed physicians at least 3 times, and nearly a third of these patients believe there is "no solution" for their pain. But is that true? Do we truly have "no solution" to offer many people who live with pain?

In reality, the treatment of pain is very often achievable; the key is education. **I am pleased to announce a new educational initiative, the *Center for the Treatment of Pain***. This peer-to-peer outreach program is designed to provide clinicians with simple, practical, and balanced information on multiple aspects of treating pain. As chair of this new program, I have assembled a team of colleagues and experts specially selected to deliver the best educational programs possible—created for clinicians, by clinicians.

The enclosed clinical bulletin—the first in a series of educational pieces to be offered through this initiative—outlines the multifactorial nature of chronic pain and offers helpful strategies for its initial assessment, diagnosis, and treatment.

Our educational Web site, www.treatmentofpain.org, will provide clinicians—in both specialist and primary care settings—with free CME, case studies, and opportunities to interact with experts. We expect to launch this site very soon.

Please join us as a charter member of this community. Simply complete the enclosed response card and drop it in the mail. Together, we can help the millions of Americans suffering from pain achieve a better quality of life.

Sincerely,

Arnold J. Weil, MD
Chairperson, Center for the Treatment of Pain

National Center for Health Statistics. Health, United States, 2006 With Chartbook on Trends in the Health of Americans. Hyattsville, MD:68-71.

Pain facts and figures. American Pain Foundation Web site. 2007. Available at: http://www.painfoundation.org/age.asp?file=NewsRoom/PainFacts.htm. Accessed June 4, 2008.

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Keys to Success

Managing the Patient with Chronic Pain

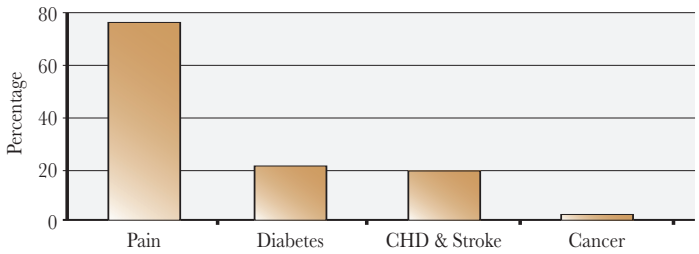
Introduction: The Epidemic of Pain

Chronic pain is extremely prevalent and has an impact that often extends well beyond the pain itself.

More than 75 million individuals in the United States experience chronic pain.[1] Chronic pain—often defined as pain lasting more than 1 to 3 months without diminishing in intensity—is one of the most common reasons Americans seek healthcare and is the most common cause of long-term disability,[2,3] impacting more Americans than diabetes, heart disease, and cancer combined (Figure 1).[4] While the economic cost is substantial, estimated at $100 billion annually in the United States,[5] the disruption to the individual's life is also significant.

Any discussion of chronic pain would be incomplete without considering the comprehensive nature of the problem. Beyond the pain, there may be adverse effects on daily activities and quality of life for patients and their families.[6] Some of these effects may include disruption of an individual's ability to concentrate, be productive, socialize, or sleep, and may lead to feelings of isolation, depression, and anxiety.[7-9]

Figure 1. Incidence of pain compared with major conditions.



CHD = coronary heart disease.

Source: Overview of American Pain Surveys. Available at: http://www.painfoundation.org/page. asp?file=Newsroom/PainFacts.htm. Accessed June 6, 2008.

Despite the widespread occurrence of chronic pain, many patients are left undiagnosed, do not achieve adequate relief, or are dissatisfied with their care. One study recently found that 1 out of 4 pain patients reported changing doctors at least 3 times in an effort to find relief for their pain.[10]

In this short bulletin, we will focus on the comprehensive nature of the problem of chronic pain, which includes sleep disturbance and other secondary and concomitant issues—important outcomes in the management of pain. We will also review effective therapies for the management of pain and treatment strategies to improve clinical outcomes. Our goal is to provide practical guidance on:

- How to distinguish chronic pain from acute pain
- Treatment choices for patients with moderate to severe chronic pain
- The impact and management of secondary and concomitant issues on clinical outcomes
- The importance of a focused pain consultation

Diagnosing Pain: When Is It Chronic?

Identifying the nature of a patient's pain and its comorbidities impacts treatment decisions and, ultimately, outcome.

Beyond the Pain—Concomitant Issues Are Common[11]

In a survey of chronic pain…

- 59% of respondents reported an impact on their overall enjoyment of life
- 77% reported feeling depressed
- 70% reported difficulties concentrating
- 74% reported their energy level is impacted by their pain
- 86% reported sleep disturbances

The management of chronic pain begins with its effective assessment and diagnosis. Far too many patients with chronic pain are not identified as such and may receive inadequate or inappropriate care. Unlike acute pain, chronic pain ceases to serve a protective function, and instead degrades health and functional capability. Left untreated, it can have profound effects on an individual's health and quality of life.

How, then, does one identify pain as "chronic?" Duration of pain alone is no longer considered sufficient information with which to distinguish acute pain from chronic pain. Assessment is still practical, however, using the following guideline: Pain is considered chronic when it extends beyond the normal period of healing and disrupts sleep and normal living.[12]

Clinical judgment is the most important component in a diagnosis of chronic pain. Table 1 identifies characteristics of acute vs chronic pain that may aid in this diagnosis (Table 1).[12-14]

Table 1. Classification of Pain: Acute vs Chronic[12-14]

Acute Pain	Chronic Pain
• Pain usually concordant with degree of tissue damage, which remits with resolution of injury	• Low levels of identified underlying pathology that do not explain the presence and/or extent of the pain
• Reflects activation of nociceptors and/or sensitized central neurons	• May occur at several sites
• Often associated with autonomic nervous system and other protective reflex responses	• Continuous or intermittent with or without acute exacerbations
	• Associated with central sensitization
	• Irritability, social withdrawal, depressed mood and vegetative symptoms (changes in sleep, appetite, libido), disruption of work, and social relationships

Clinical Goals and the Focused Pain Office Visit

Taking a thorough history can help identify secondary issues that must be addressed.

The goals of chronic pain management correspond with the comprehensive nature of the patient's needs. Focusing solely on the pain may lead clinicians to overlook important concomitant issues like sleep disturbance or psychosocial issues. These treatment goals can be summarized as follows:

- Relieve the patient's pain
- Address secondary and concomitant issues
- Improve the patient's functionality and quality of life

The pain consultation or office visit can be focused but also account for important associated conditions and issues. Although the experience of pain is subjective and cannot be easily validated or objectively measured,[12] consider assessing the following at each consultation for pain:

- Directed physical examination
- Pain history
  - Review of previous diagnostic studies and previous interventions/medication history
  - Confirmatory laboratory and radiographic procedures, when appropriate
- Impact pain has on the patient—quality of life (see callout box)
  - Social impairment
  - Missed work/school
  - Decreased productivity
- Concomitant conditions
  - Anxiety/depression
  - Sleep disturbance
  - Chronic fatigue
  - Irritable bowel syndrome
- Comorbid substance abuse disorders
  - Personal and family history of alcohol and drug use
  - Presence of psychiatric disorders

Questions to ask patients with chronic pain

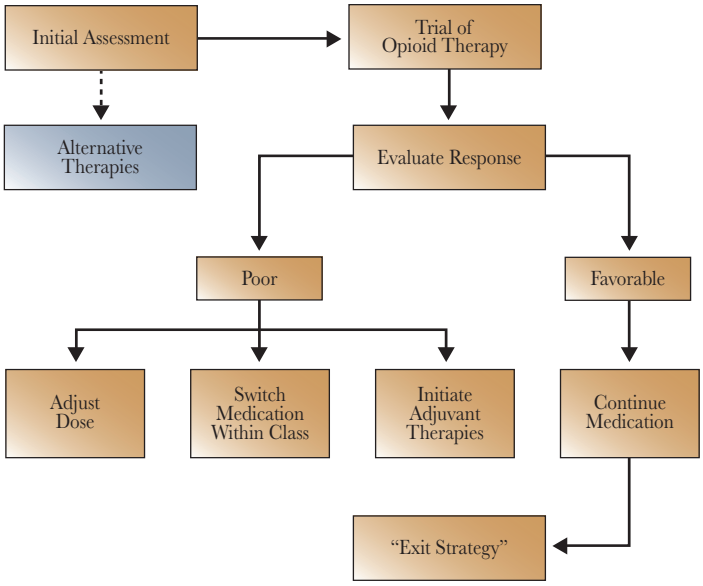
- How well controlled would you say your pain is on an average day? Do you experience episodes of breakthrough pain?
- Is your sleep affected by chronic pain? Do you have trouble falling asleep because of pain? Staying asleep?
- How do you feel when you wake in the morning—refreshed? Fatigued? Do you toss and turn at night because of the pain?
- Does chronic pain interfere with your quality of life or your activities of daily living—work, social, family?
- Is your pain worse in the morning or the evening?

Armed with the proper information, appropriate treatment decisions can be made.

Treatment of Chronic Pain and Its Comorbidities

Once a diagnosis of chronic pain has been made, the clinician and patient should agree on a treatment plan. The treatment of chronic pain ranges from monotherapy for straightforward cases to comprehensive, multidisciplinary methods for the more challenging ones. For the treatment of moderate to severe chronic pain, the American Academy of Pain Medicine (AAPM) recommends an initial trial with an opioid followed by careful reassessment (Figure 2).[15]

Figure 2. Algorithm for the treatment of chronic pain.[15]



Opioids are acknowledged as the gold standard for the treatment of moderate to severe acute and chronic pain. Although no established dosing guidelines exist for the use of opioids, an initial trial is recommended, followed by an evaluation of treatment response, any necessary adjustments to dosage or therapy, and regular follow-up. Dosages should be adjusted according to the intensity and duration of the pain. As in other therapeutic areas, patient education is a key component of optimal outcomes.

Although concerns have arisen concerning the safety of opioids and the potential for their misuse and abuse, long-term therapy with opioids is clinically proven to be both safe and effective when employed under the guidance of a skilled clinician. Importantly, clinicians need to recognize that tolerance and physical dependence may be normal consequences of sustained use of opioid analgesics and are not the same as addiction.[16] In all cases, patients must be closely monitored with appropriate drug screening and pain management agreements. This includes full disclosure and discussion of potential safety issues. Many of the pharmacologic agents used for the treatment of chronic pain carry black box warnings. Clinicians should become familiar with the specific safety information for these agents.

When adjuvant therapy is required, multiple options are available. While an in-depth discussion of these is not in the scope of this bulletin, Table 2 provides an overview of nonopioid therapy classes.[17-27]

Table 2. Nonopioid Analgesia for Chronic Pain[17-27]		
Category	Example(s)	Comments
Acetaminophen		Not anti-inflammatory Heavy use may cause nephro-and hepatotoxicity
Nonselective NSAIDs	Ibuprofen, aspirin, naproxen, ketorolac	Higher risk of gastrointestinal toxicity
Cyclooxygenase-2-selective inhibitors	Celecoxib	Less gastrointestinal toxicity than with nonselective NSAIDs Higher risk of cardiovascular events
Topical therapies	Capsaicin cream Lidocaine 5% patch	Relieves pain but may burn skin Minimal risk of systemic exposure or drug interactions
Antidepressants Tricyclics SSRIs Other	Amitriptyline, imipramine Fluoxetine, Sertraline Duloxetine	Analgesic mechanism unrelated to antidepressant mechanism Inconsistent analgesia Safe, effective for fibromyalgia
Atypical antipsychotics	Olanzapine, clozapine	Some analgesic benefit but high rate of side effects
Antiepileptics First generation Second generation	Carbamazepine, phenytoin Gabapentin, lamotrigine, pregabalin	Effective in neuropathic pain. Effective in pain, lower side-effect profile than first generation
α_2-Adrenergic agonists	Clonidine Tizanidine	For neuropathic pain refractory to other treatment Effective in headache, back, neuropathic, myofascial pain

NSAID = nonsteroidal anti-inflammatory drug; SSRI = selective serotonin reuptake inhibitor.

Beyond pharmacotherapy, an interdisciplinary approach may be required for some patients, including the administration of localized anesthetic, nerve blocks, acupuncture, electrical stimulation, physical therapy, surgery, psychotherapy, relaxation techniques, biofeedback, and behavior modification. In the majority of cases, however, an assessment of need for adjuvant therapies or alternative approaches can be made after an initial trial and titration of opioid therapy is made.

Clearly it is the *patient*, not just the *pain*, that must be assessed and treated. Foremost to the clinician, this includes attention to secondary and concomitant issues. The next section will focus on practical steps that can be taken to help improve the most common secondary effect of chronic pain: sleep disturbance.

Managing the Secondary Effects of Chronic Pain—Better Outcomes, Day and Night?

Sleep disturbance is a major secondary effect of chronic pain.

The disruption of normal sleep is an incredibly important secondary effect of chronic pain. The complex relationship between sleep, pain, fatigue, depression, and other factors is difficult to characterize. For example, intensity of pain and sleep disturbance appear to have a bidirectional relationship: pain is associated with worsening sleep and sleep problems intensify the perception of pain.[28, 29] A complex of negative outcomes is also known to occur concomitantly with pain-associated sleep disturbance (Table 3).

Table 3. Concomitant Issues Associated With Sleep Disturbance[30]
Daytime fatigue and somnolence
Mood disturbance
Impaired ability to perform daily activities
Likelihood of clinical depression
Lack of reparative or restorative functions of sleep may impair healing and lead to increased/chronic pain
Compromised coping mechanisms

In patients currently on opioid therapy, prevalence of sleep disturbance across multiple measures has been reported in the clinical setting. One study showed prevalence of 47% to 66.5% disruption across 15 sleep quality criteria in patients with chronic pain. This was within 2% to 9% of scores from a group studied with clinical insomnia and over 1 standard deviation greater than normal healthy adults.[30] Although prevalence data vary, in practice one is likely to see sleep disturbance in a majority of patients with chronic pain. For this reason, it is important to include a discussion of sleep during each focused pain consultation.

The mechanism for this sleep disturbance is not fully understood and is likely multifaceted. Addressing sleep disturbance in clinical practice is a complex undertaking that certainly cannot be reduced to a single approach. One hypothesis with practical implications for the clinician, however, is that nighttime administration of acute opioid therapy may in fact be disruptive to sleep.[31] In the next section, this concept will be explored.

Can drug therapy selection improve sleep in patients with chronic pain requiring opioid therapy?

When evaluating options for maintaining control of pain and improving disturbed sleep, the differences among available opioid therapies become significant and may provide evidence-based strategies to improve sleep. The use of sustained-release opioids (SRO), as opposed to immediate-release formulations, may be responsible for improvements in both pain and sleep symptoms. Table 4 identifies currently available opioid therapies and their dosage schedules.[32-38]

The drug delivery systems of sustained-release opioid formulations greatly impact the analgesic properties and pharmacokinetics of the opioids.[39] For this reason, they should not be approached as a homogenous group.

Due to the complex and often subjective nature of both pain and sleep, any studies aimed at measuring sleep improvement with opioid therapies have limitations. For example, only minimal data regarding opioid use and sleep disruption come from objective sleep labs rather than subjective survey-based studies. An open-label, randomized, parallel-group multicenter study presented by Rauck et al at the 2006 American Pain Society annual meeting compared the efficacy, safety, and effect on important quality of life parameters of once-daily extended-release morphine sulfate capsules (Avinza®, A-MQD) and twice-daily controlled-release oxycodone HCl

Table 4. Opioids for Chronic Pain[32-38]

Therapy (Brand Name)	Doses Available	Suggested Dosing
Sustained-Release		
Morphine sulfate extended-release capsules (Avinza®)	30, 60*, 90*, 120* mg	30 mg/d; ↑ ≤QOD as needed Opioid-naive patients: ↑ 30 mg q4d as needed Max: 1600 mg/d
Morphine sulfate extended-release capsules (Kadian®†)	10, 20, 30*, 50*, 60*, 80*, 100*, 120* mg	½ estimated total daily oral morphine dose q12h OR 100% q24h; ↑ ≥QOD as needed Opioid-naive patients: 10-20 mg/d ; ↑ ≤20 mg QOD
Morphine sulfate tablets (MS Contin®†)	15, 30, 60, 100* 200* mg	½ estimated total daily oral morphine dose q12h OR 1/3 q8h
Oxycodone HCl tablets (OxyContin®)	10, 15, 20, 30, 40, 60*, 80*, 160* mg	10 mg q12h as initial opioid or convert per PI; adjust dose (but not frequency) q24h-q48h
Continuous Delivery		
Fentanyl patch (Duragesic®*†)	12, 25, 50, 75, 100 mcg/h (continuous delivery)	Convert from other opioids per Table C in PI
Immediate-Release		
Morphine sulfate tablets	15, 30 mg	15-30 mg q4h
Oxymorphone HCl	5, 10 mg	5-20 mg q4h-q6h OR convert per PI

*Only for opioid-tolerant patients.
†Not evaluated for use as initial opioid.
Dosages should always be individualized to patient; consult Prescribing Information.

tablets (OxyContin®, O-ER).[39,40] During the 8-week evaluation phase of the study, A-MQD achieved significantly better results in the following:

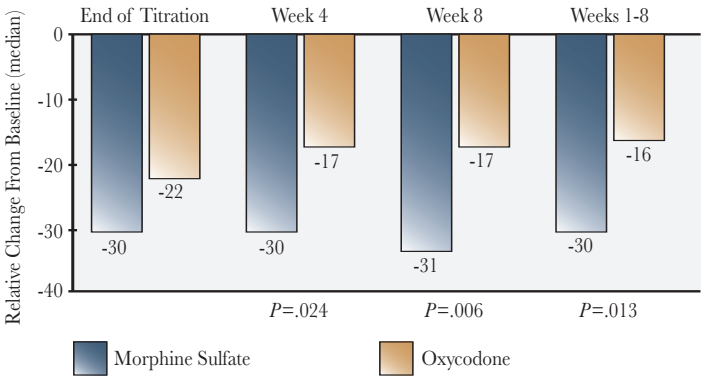
- Pain control, measured from baseline 6, 9, and 12 hours after the morning dose of each opioid
- Subjective sleep parameters, evaluated throughout the entire study period (weeks 1-8) [see Figure 3]
- Pain control achieved with lower dose (expressed in morphine equivalents)

Although it is difficult to determine the mechanism for the clinical differences in this study, the data indicate that selection of an opioid formulation may have a clinically relevant impact on sleep disturbance.

Similar results have been seen in other studies. The KRONUS-MSP trial was a prospective, randomized, open-label study with a blinded endpoint design. Patients with chronic, nonmalignant, moderate to severe pain and a history of unsuccessful pain management on other opioid therapies were randomized to either an AM or PM QD regimen with sustained-release morphine sulfate (Kadian®) for a 4-week treatment period. Over this period, a significant 29% improvement in sleep scores was seen in the group receiving extended-release morphine sulfate.[41]

Finally, a recent study of patients with chronic osteoarthritic pain was reported by Rosenthal and colleagues in the *Journal of Opioid Management*. In this study, extended-release morphine sulfate (Avinza®)

Figure 3. Relative Change From Baseline of PSQI Sleep Scores



Morphine sulfate twice daily was significantly better than oxycodone twice daily in terms of quality sleep as measured by the PSQI measured monthly at baseline and during the 8-week evaluation phase. The favorable effects of morphine sulfate on several sleep parameters were documented in a formal polysomnography trial.

was found to improve both objective and subjective measures of sleep, as well as medication acceptance and pain relief.[39] By including objective measures in a sleep lab and subjective measures, these data provide further evidence that sleep disturbance can be reduced with medical therapy.

Clinicians are encouraged to review all of the evidence comparing SRO formulations on sleep quality. Ultimately, in patients experiencing or at risk for sleep disturbance, the clinician may consider an initial trial of opioid therapy using a sustained-release formulation that can deliver a steady dose throughout the day and night.

Conclusion

Given the prevalence of chronic pain in America and the impact on the individual's quality of life, it is imperative that clinicians become well-versed in diagnosing, treating, and managing the pain and all of its secondary and concomitant issues. Success in this endeavor depends upon a directed physical examination and a thorough assessment of the patient's pain history, quality of life, concomitant conditions, and comorbid substance abuse disorders.

Since opioids are the gold standard in the treatment of both acute and chronic pain, they are recommended as a therapeutic starting point. With regular evaluation, dosages can be modified to manage the pain, and adjuvant therapies initiated as needed to address all secondary and concomitant issues. Ultimately, it is the patient who must be treated, rather than just the pain.

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Center for the Treatment of Pain

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