Abuse, Addiction, and Pain Relief
Time for Change

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The content presented in this CME newsletter was derived from a roundtable discussion held in Bethesda, Maryland on February 8, 2008 and was established by the following core faculty members:

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PROGRAM OVERVIEW

Chronic pain is undeniably a major concern for patients, healthcare professionals, and the health care system. In the absence of globally accepted guidelines, chronic pain management remains burdened with debate. At the heart of the controversy is the appropriate role of prescription medications for moderate to severe pain, specifically the role of opioid analgesics. As with any medication, selecting a prescription pain medication involves assessing risks and benefits. Unlike the risks of most other classes of medications, the risks of opioid pain medications also include the potential for abuse and diversion to illicit channels of distribution for illegal use. Over the years, increasing media attention to the risks of these agents has tended to cloud objectivity and has helped perpetuate misunderstandings of the actual benefits and risks of prescription analgesics. Extensive ongoing surveillance data support the evaluation of the risk of abuse and diversion from prescription medication as manageable. All healthcare professionals have a responsibility to identify potential abuse while ensuring that patients in need continue to have full access to medications that will provide optimal relief. An understanding of the range of opioid agents including available formulations and novel therapies, coupled with an understanding of medication risks and benefits, including the data on drug abuse and diversion, will allow physicians to assess and select the best possible agent to improve the quality of life for their patients with chronic pain.

This program imparts a summary from the proceedings of a roundtable expert discussion held in Bethesda, Maryland, on February 8, 2008.

MEDIA: NEWSLETTER

TARGET AUDIENCE

This activity has been designed to meet the educational needs of clinicians involved in the care of patients with chronic pain.

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2) study the educational activity;
3) complete the posttest by recording the best answer to each question in the answer key on the evaluation form;
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ABUSE, ADDICTION, AND PAIN RELIEF

Time for Change

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INTRODUCTION

Chronic pain is a pervasive problem, affecting approximately 16%–23% (50–70 million) of Americans and impacting their physical, psychological, and social well-being.[1] Chronic pain also results in a heavy economic and social burden for both the individual patient as well as society as a whole. Patients may unrealistically believe that chronic pain can be cured; however, they frequently are forced to accept that their pain is actually a chronic disease. Finding the right combination of treatments and therapies to bring people back to their maximum functioning secondary to decreased pain often takes a long time.

Opioids are a cornerstone in the treatment of moderate to severe chronic pain. Yet, despite the effectiveness of these medications, physicians unfortunately are often reluctant to prescribe them, and the prevalence and incidence of undertreatment of chronic pain remains high.[1] This publication is the result of a roundtable discussion among some of the leading pain and addiction experts in the country. It represents a consensus regarding the impact of chronic pain, issues surrounding prescribing opioids, opioid-related adverse effects, and newer treatment approaches, formulations, and medications that may address some of these issues.

IMPACT OF CHRONIC PAIN

Pain is characterized as being either acute or chronic. Acute pain is an adaptive, beneficial response necessary for the preservation of tissue integrity. It comes on quickly and can be severe, but it usually lasts for a short period of time (0-3 months).[2] Chronic pain, however, is pain that has outlived its usefulness and persists for 3 months or longer.[2] Chronic pain may be associated with low levels of identified pathology that do not adequately explain the presence or extent of the pain.[2] Chronic pain is a common medical condition that affects 50 million Americans of all ages[2,3] and poses a significant burden in terms of patient suffering and health care costs. Most individuals with chronic pain classify their pain as being severe or very severe and have been suffering for a significant amount of time—on the average of 5 years or more.[4] Patients suffering from chronic pain have reported poor sleep, anxiety, depression, loss of independence, and interference with work and personal and professional relationships.[2,5,6] Many patients do not seek help because they believe nothing can be done to help them.[4] When these facts are taken together, it becomes obvious that pain affects the whole person and dramatically impacts quality of life, including physical, psychological, and biopsychosocial domains.

The economic burden of chronic pain is significant. Common pain conditions, including arthritis, back pain, headache, and other musculoskeletal conditions, cost businesses approximately $61.2 billion each year. Chronic pain accounts for up to 13% of lost productive time within a 2-week period, and approximately 77% of lost productive time due to reduced performance is caused by chronic pain.[7] Health care costs add billions more to this figure. For example, low back pain alone results in more than $90 billion in direct costs each year.[8] Thus, chronic pain not only affects many aspects of the patient's life but also has significant impact on society as a whole. Therefore, it is imperative that both physicians and patients focus on obtaining adequate relief of pain.

CHALLENGES IN TREATMENT AND MANAGEMENT

Many effective pharmaceutical options are available for the treatment of pain, including over-the-counter medications, such as acetaminophen and nonsteroidal anti-inflammatory drugs, and prescription pain relievers, such as opioids. However, despite the plethora of treatment options, some surveys have found that 70% of adults receiving pain medication continued to report persistent pain.[9] Moreover, less

EDUCATIONAL OBJECTIVES

Upon completion of this activity the participants should be better able to:

- Specify the impact of the undertreatment of pain and inadequate pain relief
- Identify key issues surrounding the treatment of chronic pain with scheduled and non-scheduled opioid analgesics
- Outline the risk/benefit ratios of current and future prescription analgesics and formulations
- Cite the federal regulations regarding prescription pain medications
- Review national surveillance/monitoring data
- Identify appropriate roles of the primary care physician and pain specialist in the management of pain patients

than half of patients with chronic pain—about 21.6 million people—take a prescription pharmacotherapeutic agent to manage their pain.[10]

In order to effectively treat and manage chronic pain, healthcare providers must clearly understand the key components of initial evaluation with a differential diagnosis and a treatment plan with regular reassessment of pain scores and level of function. This is especially important for primary care practitioners who are typically the first to assess and manage patients with moderate to moderately severe chronic pain.[4] Statistics show that almost half of all patients being treated for noncancer–related chronic pain have changed physicians at least once, with approximately 25% changing physicians more than 3 times because of inadequate pain relief, excessive medication side effects, or inadequate response from the physician.[4]

Getting pain under control also takes time. Up to 70% of patients with severe pain—and just over half of those with moderate pain—require at least 6 months to get pain under control.[4]

TREATMENT MODELS

Chronic pain may not be adequately managed in the absence of clear treatment algorithms. Therefore, several models exist for the conceptual and organizational management of chronic pain. Conceptual models of chronic pain include the Biomedical Model in Chronic Pain and the Biopsychosocial/Neurobehavioral Model. Organizational models of chronic pain include the Tertiary Sequential Care Biomedical Model, the Multidisciplinary Biobehavioral Pain Center Model, the Pain Medicine and Primary Care Community Rehabilitation Model, and the Managed Primary Care Model.[11,12]

The *Biomedical Model in Chronic Pain* presupposes that pain is caused by a specific injury or disease and can be relieved by identifying and treating that cause. This model is often inadequate in clinical practice because frequently no clear cause of a patient's pain can be determined. Pain and morbidity may thus persist without the biomedical model offering any solutions.[11]

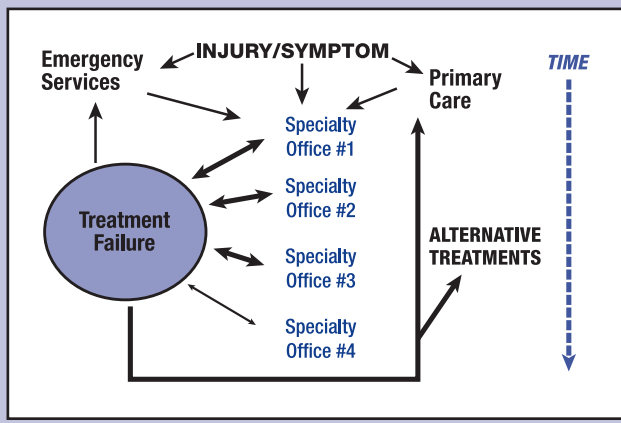
The *Biopsychosocial/Neurobehavioral Model* is based on the premise that chronic pain is not necessarily caused by a single pathologic entity; it is the most appropriate model for understanding the clinical course of pain. This model addresses several dimensions of chronic pain in one treatment program. However, implementing the Biopsychosocial/Neurobehavioral Model is difficult in clinical practice as pain is multidimensional and treatment requires an understanding of its physical, psychological, and social factors.[11] A lack of training in medical school provides some explanation why medicine has not moved beyond a biomedical model.

The *Tertiary Sequential Care Biomedical Model* tries to define the patient in clinicopathological methods by a sequence of referrals to specialists (Figure 1).[12,13] This model is prevalent in cities with major medical centers and has been the predominant model for decades. For example, a patient is injured and goes to the emergency room, a primary care physician, or, depending on the patient's health plan, a specialist. If the patient's pain is not controlled, he or she is referred to the next provider down the line. This model can expose patients to many unnecessary diagnostic and treatment procedures.[12]

Under the *Multidisciplinary Biobehavioral Pain Center Model*, the patient should be examined by health-care providers with different yet complementary areas of expertise, thus ensuring that no important details are overlooked (Figure 2).[12,13] This model is cost-effective for patients who require the attention of a large team composed of several specialists. However, multidisciplinary centers are not universally available. In addition, patients are usually managed by a pain medicine physician, and referral occurs late in the clinical process.[12]

FIGURE 1

THE TERTIARY SEQUENTIAL CARE BIOMEDICAL MODEL[13]

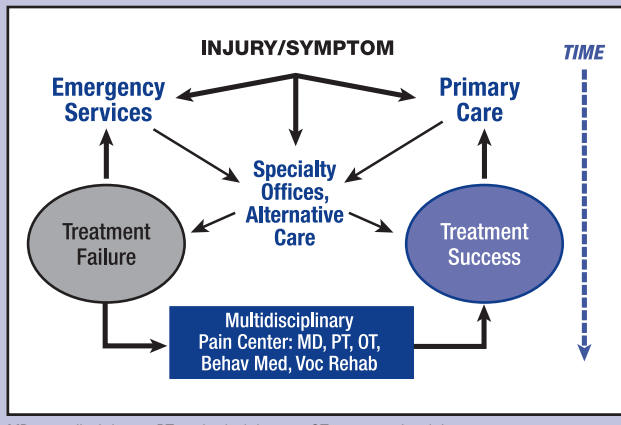


Medical Clinics of North America: Gallagher "Chronic Pain" ©1999, pp. 555-583, Figure 1. Used with permission of Elsevier Inc. All rights reserved.

The *Pain Medicine and Primary Care Community Rehabilitation Model* calls for physicians with expertise in pain medicine to staff a pain center—located in easily accessible locations throughout the community—that supports a network of primary care physicians, behavioral specialists, and physical therapy programs (Figure 3).[12,13]

FIGURE 2

THE MULTIDISCIPLINARY BIOBEHAVIORAL PAIN CENTER MODEL[13]



MD = medical doctor; PT = physical therapy; OT = occupational therapy; Behav Med = behavioral therapy; Voc Rehab = vocational rehabilitation.

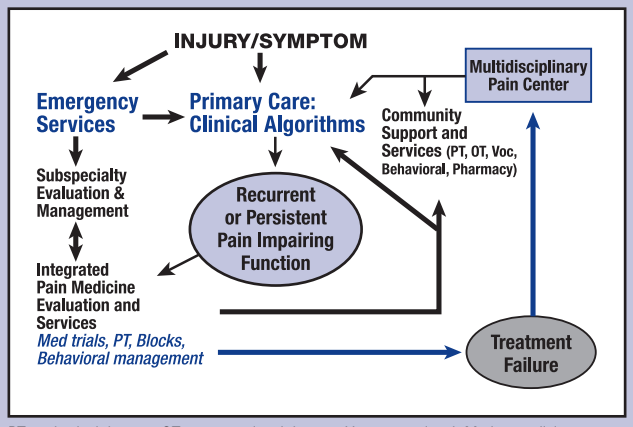
Medical Clinics of North America: Gallagher "Chronic Pain" ©1999, pp. 555-583, Figure 2. Used with permission of Elsevier Inc. All rights reserved.

A pain medicine physician manages the patient flow through services (eg, behavior pain management, rehabilitation, medication trials, invasive procedures).[12]

Under the *Managed Primary Care Model*, there is one physician who is designated to provide care to the patient (Figure 4).[12,13] However, this physician often has limited training specific to pain. In

FIGURE 3

THE PAIN MEDICINE AND PRIMARY CARE COMMUNITY REHABILITATION MODEL[13]

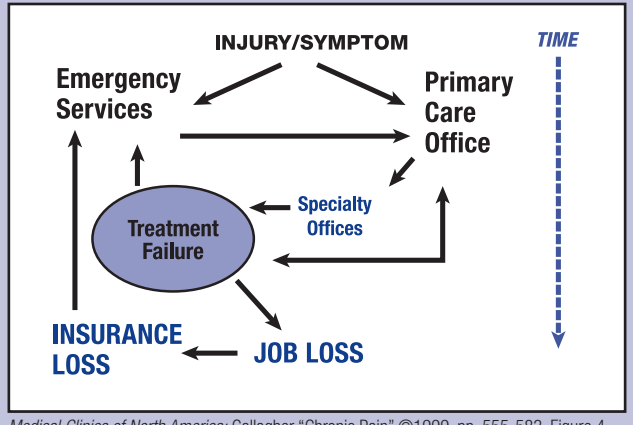


PT = physical therapy; OT = occupational therapy; Voc = vocational; Med = medicine.

addition, the accepted standard of care is often not approved by the insurance adjustors, and physicians may be discouraged from sending patients to specialists, resulting in cost shifting among various sectors.[12]

FIGURE 4

THE MANAGED PRIMARY CARE MODEL[13]



TREATMENT

Opioids have long been a mainstay in the treatment of both nociceptive and neuropathic moderate to severe chronic pain, and their role in pain management is widely accepted.[14] Stable doses of scheduled opioids can offer patients with noncancer chronic pain satisfactory analgesia with only a minimal risk of addiction in appropriate patients.[15]

The clinical impression is that most patients with chronic pain may benefit from a long-acting or immediate-release (IR) opioid in modified delivery systems secondary to 24/7 stable opioid blood levels since it offers continuous pain relief, fewer sleep disturbances, fewer problems with patient compliance, and fewer reported side effects than do other treatment options. However, patient response to treatment with opioids is highly variable, and physicians must be aware of the range of commonly available opioid treatment options, including appropriate dosing regimens and levels for treatment initiation and titration.[14] In addition, when using opioids, physicians must have both a clear entrance and a clear exit strategy at the initiation of therapy.[16]

The use of opioids has been associated with somnolence, confusion, nausea, and vomiting.[17] Treatment with opioids results in the activation of the chemoreceptor trigger zone for emesis, reduces gastrointestinal motility, and increases vestibular sensitivity.[14] Constipation, especially in elderly patients, may limit the usefulness of opioids in treating chronic pain in this population.[18] As with any treatment, the potential side effects must be weighed against the possible benefit. Adjusting the dose or changing the opioid selection may reduce side effects and achieve the right balance with analgesia.

ABUSE

The true extent of abuse of prescription analgesics in the United States is unknown. However, it is known that for an estimated 10% of US patients being treated for drug abuse, prescription drugs are the principal drug of choice.[19] Nonmedical use of prescription drugs is the second most prevalent category of drug abuse after marijuana, and 56% more Americans abuse prescription drugs than abuse cocaine, heroin, hallucinogens, and inhalants combined.[19] The high prevalence of prescription abuse may be associated with the fact that the management of chronic pain has resulted in an exponential growth in the amount of prescriptions written for controlled substances, with estimates as high as 90% of patients with chronic pain receiving opioids.[19] Thus, increased availability of opioids may be driving the increased rates of abuse.

Rates of addiction or abuse resulting from long-term opioid therapy have been difficult to establish, with estimates ranging from 3% to 43% in patients with chronic back pain.[20] Controversy due to the fear of addiction or abuse also surrounds the risks versus the benefits of opioids in long-term therapy.[15]

Novel medications are being developed that avoid some of the side effects and reduce the potential for abuse currently associated with opioid use. Extended-release tablets and mechanically stable tablets represent 2 approaches for novel analgesics. Because routes of administration with rapid drug delivery to the brain (eg, smoking, inhalation, intravenous) are associated with higher abuse potential in genetically susceptible individuals, controlled-release or delayed-release profiles (or a combination of both) are aimed at slowing the drug in entering the brain as a way of reducing abuse potential.[21-23] These formulations also offer sustained efficacy, fewer analgesic gaps and better tolerability, and provide better patient adherence, while promising potentially less abuse and diversion.[24]

Many abusers crush extended-release oxycodone, allowing the full dose of the drug to be released all at once. Mechanically stable tablets may circumvent this behavior by preventing the tablet from being crushed. A study examined whether a novel controlled-release formulation that is difficult to crush would be less preferred and have a lower street value to abusers who currently tamper with oxycodone.[25] Participants, who had a history of abusing oxycodone, were provided with requested tools to tamper with a placebo that was designed to prevent crushing. The majority (90%) preferred regular oxycodone to the test tablet, and they estimated that the monetary

worth of the test tablet would be only 57% of that of standard oxycodone. Thus, mechanically stable tablets may be an effective way to reduce the abuse potential of oxycodone by making the tablets less desirable to those who would abuse.

NEW MEDICATIONS WITH NOVEL MECHANISMS OF ACTION

Newer drugs that interact with μ-opioid receptors have novel mechanisms of action. One class of agents, peripherally acting μ-opioid receptor (PAMOR) antagonists, includes alvimopan and methylnaltrexone. Conventional opioid antagonists can reduce or eliminate the adverse effects associated with opioids, but all block analgesic effects. Since PAMOR antagonists are restricted from crossing the blood-brain barrier, they can mitigate the undesirable gastrointestinal (GI) side effects associated with opioids, while sparing centrally mediated analgesia.[26,27] Another agent, tapentadol, is a novel, centrally acting analgesic with a dual mode of action: μ-opioid receptor agonism and noradrenaline reuptake inhibition.[28,29] This dual mechanism of action allows for a broad and efficacious analgesic profile. These newer agents hold the promise of reduced opioid-related GI side effects, while maintaining adequate analgesia.

Alvimopan

Alvimopan is a μ-opioid antagonist that is restricted from crossing the blood-brain barrier. This characteristic allows alvimopan to block peripheral GI side effects (eg, ileus, constipation) associated with opioids without compromising the central nervous system analgesic activity of coadministered full opioid agonists. Opioid bowel dysfunction (OBD) is associated with multiple GI symptoms (eg, pain, discomfort, bloating, constipation, gastroesophageal reflux disease with persistent symptoms), possibly leading to nausea, vomiting, fecal impaction, and impaired absorption. Clinical studies have shown that alvimopan reduced postoperative ileus, reversed OBD, and normalized GI side effects in patients receiving long-term opioids.[27]

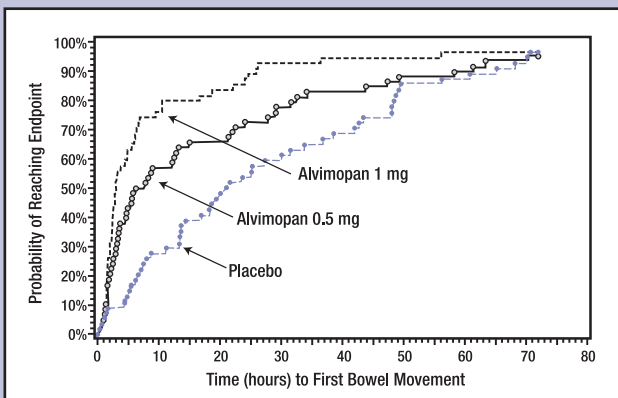
One randomized, placebo-controlled trial involved 168 patients (n=148 for chronic pain; n=20 for opioid dependence) who had received opioid therapy equivalent to ≥10 mg morphine orally for ≥1 month. Patients received placebo, 0.5 mg alvimopan, or 1 mg alvimopan orally once daily. The study examined the proportion of patients with ≥1 bowel movement within 8 hours of receiving alvimopan (Figure 5).[30] Results showed that treatment with alvimopan reversed GI dysfunction, with a higher proportion of patients responding to treatment with alvimopan than with placebo.[30]

Methylnaltrexone

Similar effects on GI transit time have been seen with methylnaltrexone, which is now approved in a subcutaneous formulation by the US Food and Drug Administration for treating opioid-induced constipation. In one study, oral methylnaltrexone prevented the delay in GI transit time caused by a single dose of morphine.[31] Participants who received 6.4 mg/kg of enteric-coated methylnaltrexone had greatly reduced intravenous morphine-related delays in oral-cecal transit time and lower plasma concentrations of the drug.[31] In other studies, subcutaneous methylnaltrexone similarly blocked morphine-induced delays in oral transit time or stimulated laxation significantly faster than did placebo in opioid-dependent patients who did not have preexisting withdrawal symptoms or increasing pain scores.[32,33] Methylnaltrexone is also capable of accelerating GI transit in chronic opioid users.[31] A double-blind, randomized, placebo-controlled trial enrolled patients from a methadone maintenance program who were experiencing methadone-induced constipation. Intravenous methylnaltrexone reversed opioid constipation in these patients, with laxation occurring immediately after administration on day 1 and day 2. Taken together, these studies provide evidence that alvimopan and methylnaltrexone are novel peripherally acting μ-opioid antagonists that may be useful adjunctive therapies for patients with chronic pain to relieve opioid-induced constipation.

FIGURE 5

TIME TO FIRST BOWEL MOVEMENT WITHIN 8 HOURS OF RECEIVING ALVIMOPAN[30]



Journal of Pain: Paulson ©2005, Vol 6, pp. 184-293, Figure 3. Used with permission of Elsevier Inc. All rights reserved.

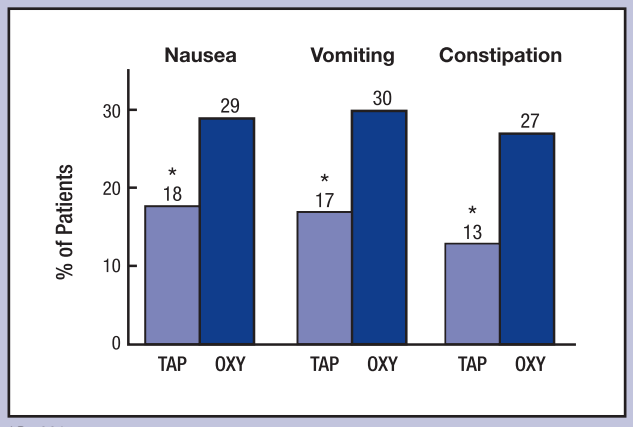
Tapentadol

Preclinical studies have demonstrated the analgesic effectiveness of tapentadol in a number of animal models of pain, and there is no indication of substantial analgesic tolerance.[28,29] Tapentadol is a novel analgesic with a dual mode of action comprised of μ-opioid receptor activation and norepinephrine reuptake inhibition. The parent compound of tapentadol is active, not a metabolite; therefore, it does not require the cytochrome P4502D6 metabolic pathway and thus has a lower potential for drug-drug interaction.[34]

A randomized, double-blind, placebo-controlled phase 3 trial enrolled 849 patients with low back pain or osteoarthritis of the knee or hip, 679 of whom received either 50 or 100 mg tapentadol immediate release every 4 to 6 hours as needed and 170 of whom received 10 to 15 mg oxycodone IR every 4 to 6 hours as needed.[35] Mean pain intensity scores were 4.9 for tapentadol IR compared to 5.2 for oxycodone IR. The respective incidence of treatment-emergent side effects was lower in the tapentadol IR group than in to the oxycodone IR group (76.3% vs 82.9%). Tapentadol IR treatment resulted in a lower incidence of nausea, vomiting, and constipation than did treatment with oxycodone (Figure 6).[35] In another study, patients were assessed for withdrawal symptoms using the Clinical Opioid Withdrawal Scale (COWS) and the Subjective Opioid Withdrawal Scale (SOWS) 2 to 4 days after cessation of therapy.[36] Using the COWS scale, a larger percentage of patients reported no withdrawal symptoms (83% vs 71%), and mild or moderate symptoms were reported by a significantly lower percentage of patients in the 50- to 100-mg tapentadol group (17.0% and 0.3%, respectively) compared with the 10- and 15-mg oxycodone group (25.8% and 3.0%, respectively;

FIGURE 6

GASTROINTESTINAL TOLERABILITY OF TAPENTADOL IMMEDIATE RELEASE (TAP) VS OXYCODONE (OXY)[35]



*P<.001

P<.05). Using the SOWS scale, patients in the tapentadol group had lower SOWS scores than those in the oxycodone group (6.9 vs 8.7, respectively).

Similar results were seen in a double-blind, active- and placebo-controlled multicenter phase 3 trial that randomized 666 patients with osteoarthritis of the hip or knee who were considered eligible for joint replacement surgery due to end-stage degenerative joint disease.[37] Patients received tapentadol IR 50 or 75 mg, oxycodone IR 10 mg, or placebo. The primary end point was the sum of pain intensity difference (SPID) over the first 5 days. Pain intensity was assessed twice daily each day by patients answering the question "What is your pain level for the past 12 hours?" and rating pain on an 11-point scale. Both tapentadol IR doses and oxycodone resulted in significant differences from placebo for 5-day SPID (P<.001 for all comparisons). Prespecified efficacy comparisons of 5-day SPID showed that both tapentadol IR doses provided statistically comparable efficacy to that of oxycodone IR. GI side effects were less common in patients taking tapentadol IR 50 and 75 mg (29% and 40%, respectively) than in those taking oxycodone IR (69%).[37] These trials showed that tapentadol IR substantially improved GI tolerability compared to oxycodone IR at doses that provided similar relief.[35-37]

PAIN AND THE PRIMARY CARE PHYSICIAN

Chronic pain, like other chronic diseases, lends itself to disease management. Primary care physicians are an initial point of contact for patients with chronic pain, and, for the most part, these physicians are equipped for disease management. However, in the instance of difficult cases, patients would most likely benefit from being referred to pain specialists, as per the triage system in (universal precautions in pain medicine) (Table 1).[16]

Statistics show that primary care practitioners manage half of all patients with pain, nearly half of whom have very severe pain.[4] The remaining half of these patients are treated by orthopedic surgeons, rheumatologists, neurologists, or chiropractors, among others. Although primary care physicians are on the frontline of pain management, many are inadequately trained on how to treat chronic pain effectively. Nearly 90% of physicians rate their education in pain management as poor, and more than 70% rate their residency training in pain management as fair or poor. Surveys show that 76% of physicians believe a lack of familiarity with patient assessment is a major barrier to effective pain management, and 61% are reluctant to prescribe analgesic medications.[17] These statistics suggest that training in pain management for most physicians is inadequate. A general comfort level is necessary for physicians to begin to feel at ease with opioid dependent pain patients.

TABLE 1

UNIVERSAL PRECAUTIONS FOR OPIOID USE[16]

1. Diagnosis with appropriate differential: treatable causes for pain should be identified.
2. Psychological assessment including risk of addictive disorders: physicians should inquire into past personal and family history of substance misuse.
3. Informed consent (verbal vs written/signed): physicians must discuss treatment with patients and answer any questions about treatment, including risk and benefits.
4. Treatment agreement (verbal vs written/signed): expectations and obligations of both patient and treating practitioner need to be clearly outlined.
5. Pre- and postintervention assessment of pain level and function: treatment should begin with a trial of medication, and the physician should document pretreatment pain scores and level of function.
6. Appropriate trial of opioid therapy ± adjunctive medication: opioids should not be thought of as the treatment of choice but also must not be the last resort.
7. Regular reassessment of pain score and level of function: this helps document rationale to continue or modify treatment.
8. Regularly assess the "Four A's" of pain medicine (*Analgesia, Activity, Adverse reactions, and Aberrant behavior*): this helps direct therapy and support pharmaceutical options.
9. Periodically review pain diagnosis and comorbid conditions, including addictive disorders: the underlying illness may evolve, pain evolves, and diagnostic tests change over time; therefore, treatment needs to be reviewed and modified if necessary.
10. Appropriate and accurate documentation: thorough documentation is medicolegally indicated and in the best interest of both doctor and patient.

The reluctance to prescribe analgesics presents a serious barrier to the treatment of pain. Many physicians have a negative attitude about opioids. This hesitancy to prescribe opioids for chronic pain is often due to poor assessment skills and insufficient training as mentioned earlier.[17,18] However, physicians may also feel intimidated by regulatory scrutiny and the possibility of addiction sometimes associated with the use of opioids.[17]

In certain situations, primary care physicians should consider referring patients to a pain specialist to verify and support the current treatment approach and plan. These situations include when the diagnosis is uncertain, psychiatric issues are uncontrolled, behavior related to opioids results in medication issues, and/or primary care physicians are uncomfortable with treating pain. Under these circumstances, a pain specialist can serve as a consultant to other physicians by directing a multidisciplinary team, prescribing pain-relieving medications and rehabilitative services, performing pain-relieving procedures/interventional therapy, and counseling patients and families. Thus, in many instances, a pain specialist may be better qualified to handle certain patients with chronic pain.

RISKS

As previously stated, many primary care physicians are reluctant to prescribe opioids because they are concerned about patients becoming addicted. Efforts to define and quantify opioid addiction are hampered by inconsistent use of addiction terminology.[38,39] Primary care physicians need to be able to distinguish between physical dependence, tolerance, and addiction. Not doing so may lead to inadequate treatment, diagnostic confusion, provider's false assumption of addiction, and possible premature discontinuation of opioid therapy, resulting in poor pain management and unnecessary suffering.[39,40]

Patients being treated with opioids are at risk for developing tolerance, physical dependence, and addiction. Illicit users progress rapidly to the point where dependence and addiction are indistinguishable, whereas progression in patients with pain is subtle, with addiction emerging as a distinct syndrome that is less obvious and more difficult to identify.[38] In the patient who has pain with co-morbid condition(s), aberrant behavior may be the result of inadequate relief, poor coping skills, drug abuse/addiction, or even criminal behavior. In fact, identifying aberrant behavior is usually easier than interpreting the meaning behind it.[16]

Tolerance is the result of repeated exposure to a drug that results in decreased effectiveness of the drug; therefore, more of the drug is needed to achieve the same effect.[41] Patients may also develop tolerance to some adverse effects of opioids, such as sedation and nausea, but not to others, such as constipation.[14,42] Since tolerance to opioid-induced side effects can develop at different rates, developing tolerance to some of these effects may unmask others and alert the patient and physician to potentially harmful drug-induced side effects.[42]

Physical dependence is an adaptation of the body that requires the maintenance of a specific level of drug in the body.[42,43] Withdrawal syndromes can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.[41] This pharmacologic effect is typical of opioids and is not considered to be an unmanageable clinical problem since it can be treated by gradually tapering the opioid dose, rather than abruptly stopping the medication.[42,43]

Addiction is a chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. The American Pain Society characterizes addiction as the presence of one or more of the following behaviors: impaired control over drug use, compulsive use, continued use despite harm, and craving.[41] Addiction results from the intrinsic reinforcing effects of opioids and tends to be more prominent in patients with predisposing genetic, social, or psychosocial triggers.[42,43]

Importantly, physicians should recognize that physical dependence is not the same as addiction.[14,39] Patients can be dependent and have withdrawal symptoms without being addicted, or they can be physically dependent without the compulsive drug-seeking behavior that is the hallmark of addiction or be addicted without physical dependence, as with many cocaine addicts.[14,44] Sometimes, patients with pain will exhibit behaviors, often called red flags, that mimic behaviors characteristic of addiction. This "pseudoaddiction" is drug-seeking behavior that mimics the aberrant behavior of true addiction but results from attempts to alleviate undertreated pain. Instead of terminating treatment, physicians should question patients about the behaviors as they are often the result of undertreatment.[40] Physical dependence is a neuropharmacologic phenomenon, whereas addiction is both a neuropharmacologic and a behavioral phenomenon.[45]

Pain and addiction can coexist; some patients with pain have concurrent addictive disorders that complicate treatment (eg, alcohol dependence with peripheral neuropathic pain). Failure to treat both conditions will undoubtedly lead to frustration and poor outcomes in both domains.[46] Patients with opioid addiction can be prescribed opioids but only with careful monitoring and boundary setting before writing the first prescription based on mutual trust and respect. Limits may include no early refills, using only one pharmacy to fill the prescription, no automatic refills, and random urine testing. Whereas acute pain can be treated in a patient with an underlying active addictive disorder, the successful treatment of a complaint of chronic pain in the face of an active untreated addiction is unlikely.[14] Therefore, when using opioids to treat chronic pain, physicians may identify the opioids as the problem, the solution, or a mix of both depending on the frame of reference used.[16]

Some physicians suffer from "opiophobia." They are hesitant about being aggressive with opioid treatment because they fear iatrogenic addiction, regulatory sanctions, or jeopardizing their practice or medical license. Iatrogenic addiction occurs when a patient without a personal or family history for alcohol or drug addiction or abuse is appropriately prescribed a controlled substance and subsequently in the therapeutic course meets the diagnostic criteria for addiction to that substance. However, strategies exist that can be implemented to reduce the risks associated with prescribing opioids and thereby minimize opiophobia.

Universal Precautions in Pain Medicine

The term "universal precautions" originated from the infectious disease model, where health care providers could not reliably assess the risk of infectivity during the initial assessment. Since lifestyle, past history, and past aberrant behavior, such as noncompliance, were unreliable indicators, taking a minimum level of precaution with all patients was necessary. This method is being proposed to the pain community as there is no definite test to predict which patient will do well on opioids; it therefore makes sense to take universal precautions with all patients with pain.[16]

A 10-point assessment can be used for all patients with persistent pain and may reduce the stigma of opioid use, improve patient care, and reduce the overall risk of pain management (Table 1, page 5).[16]

Another method of reducing risk, and one that should be used with every patient, is a treatment plan. The treatment plan should state the objectives of treatment, define treatment success, list any additional diagnostic evaluations or consultations, and outline any other treatments that may be needed. It should also state how treatment will be adjusted to meet the patient's individual needs.[47] Successful treatment and a successful treatment plan require that physicians develop a relationship with their patients based on trust. Treatment agreements should not be based on preconceived notions and should not be unduly influenced by a patient's history.

However, patients do often display aberrant behaviors, and the more aberrant behaviors, the more likely the person is to abuse or be addicted to drugs. However, patients not abusing may also exhibit these behaviors.[48] How then do physicians identify patients who are truly at risk for abuse and addiction?

Several tools exist for assessing a patient's risk for becoming addicted. One, the Opioid Risk Tool, is an office-based tool to predict probability of a patient displaying aberrant behavior. Each of the 5 questions in the self-administered interview is weighted and given a point value believed to reflect the risk relative to other risk factors. The

questions consider family and personal history of substance abuse, age, history of preadolescent sexual abuse, and depression. The tool was specifically developed to screen patients with chronic pain who will be using opioids.[48]

One of the most effective tools for screening for alcohol problems in the primary care setting is the CAGE questionnaire, which focuses on social and behavioral aspects of alcohol problems. The questionnaire asks 4 questions regarding the patient's drinking behavior. In a primary care setting, answering yes to 2 questions has a sensitivity of 77% to 94% and a specificity of 79% to 97% for current diagnosis of alcohol abuse or dependence.[49] These findings suggest that the CAGE-AID questionnaire provides an effective means of screening prospective patients with pain for a history of alcohol problems. The CAGE questions have also been adapted to include drugs (Table 2).[50] However, for substance abuse, CAGE-AID was found to be more sensitive but less specific than the CAGE, but it shows more promise for the identification of patients in primary care with alcohol and drug abuse disorders.

Urine drug testing is a useful tool in the primary care setting and plays a key role in safely managing patients with pain. It can confirm adherence to the agreed-upon medication treatment plan, diagnose a relapse or drug misuse early, and allow physicians to advocate for the patient for third-party interests. Initially, testing is done with class-specific immunoassay drug panels that typically do not identify individual drugs within a class. Basic urine drug screens evaluate cocaine metabolite, amphetamines/methamphetamines, opiates, methadone, marijuana, and benzodiazepines. Importantly, physicians should identify specific drugs and not just employ "drug class" identification. Basic urine testing is followed by a technique such as gas chromatography/mass spectrometry that can identify or confirm the presence or absence of a specific drug and/or its metabolites. When used in pain management, the presence of an unprescribed drug or illicit drug should not negate a complaint of pain as it may suggest a concurrent disorder such as addiction.[51,52] Also, office procedures using certain "dipsticks" can provide rapid identification of specific opioids, including oxycodone and buprenorphine, that are not identified by routine basic screens.

Federal and state authorities have created regulations surrounding the distribution and use of opioids and other substances in an attempt to curb abuse and diversion. The most widely known and used are regulations set forth by the Drug Enforcement Administration of the US Department of Justice, which classifies substances in 5 categories (schedule I-V), based on the substance's potential for abuse; scientific evidence of its pharmacotherapeutic effects; current scientific knowledge of the substance; history or pattern of abuse of the substance; the scope, duration, and significance of abuse; level of risk to public health; the substance's psychic or psychological dependence liability; and whether the substance is an immediate precursor of a substance that is already controlled.[53]

Some states, such as Kentucky, have gone beyond the federal regulations and have enacted guidelines and laws extending the restrictions on certain substances. For example, the Kentucky Board of Medical Licensure has created guidelines stating that controlled substances for pain can be prescribed only for a legitimate medical purpose, based on accepted scientific knowledge of pain treatment and on sound clinical grounds. In addition, the prescription must be grounded in clear documentation of unrelieved pain and must comply with applicable state or federal laws.[47]

Public and private agencies have enacted monitoring and surveillance programs in an attempt to reduce diversion.[54] The programs help law enforcement identify and prevent prescription diversion and educate physicians, pharmacists, and the public about such activities. However, each program differs with regard to which drugs are covered, how information is collected, and which agency is responsible for gathering the data. Examples of programs include the National Forensic Laboratory Information System (NFLIS), which gathers data from laboratories that handle 71% of the approximately 1.2 million annual drug cases in the United States. The NFLIS analyzes drug evidence secured in law enforcement operations nationwide and provides information on the diversion of legally manufactured drugs.[54] The Drug Abuse Warning Network (DAWN), which is operated by the Substance Abuse and Mental Health Services Administration of the US Department of Health and Human Services, collects data on emergency department visits related to drug use and drug-related deaths that are investigated by medical examiners and coroners.[55] The Researched Abuse, Diversion, and Addiction-Related Surveillance (RADARS®) System is a state-of-the-art surveillance program utilizing timely methods to assess abuse and diversion of schedule II and III opioids.[56]

In addition, as of 2006, 21 states had a prescription monitoring program in place that collects information on the prescribing, dispensing, and use of certain controlled substances, and an additional 6 states had passed legislation to create such a system.[57]

TABLE 2

QUESTIONS FOR CAGE-AID SCREENING TOOL[50]

"Have you felt you ought to **C**ut down on your drinking or drug use?"

"Have people **A**nnoyed you by criticizing your drinking or drug use?"

"Have you ever felt bad or **G**uilty about your drinking or drug use?"

"Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover (**E**ye-opener)?"

CAGE-AID = CAGE Adapted to Include Drugs.

Wisconsin Medical Journal, 1995. Reprinted with permission.

CONCLUSION

Chronic pain is a serious health issue that affects millions of patients physically, emotionally, and socially. Many treatment options, both pharmacologic and nonpharmacologic, exist, with opioids being the cornerstone of many treatment modalities. Although the risks of abuse and diversion are low among patients with a legitimate medical need, the possibility does exist. Therefore, health care practitioners should monitor not only a patient's level of pain but also any aberrant behavior, and treatment should be adjusted accordingly.

Newer pharmacologic agents with novel mechanisms of action, such as the PAMOR antagonists and tapentadol, have been developed to address the problem of opioid-related side effects. PAMOR antagonists block GI side effects, while sparing centrally mediated analgesia. Tapentadol is an efficacious analgesic with a dual mode of action that has reduced liability for GI side effects and withdrawal. Newer treatment modalities, such as extended-release tablets and crush-proof tablets, are being developed to help circumvent the risks of abuse and diversion.

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CLINICAL COURIER ABUSE, ADDICTION, AND PAIN RELIEF — Time for Change

Request for Credit

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better. Your statement of credit will be mailed to you within three weeks.

If you wish to receive acknowledgement for completing this activity, please complete the posttest by selecting the best answer to each question, complete this evaluation verification, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. Click on "Find Post-test/Evaluation by Course" on the navigation menu, and search by project ID 5422. Upon successfully completing the post-test and evaluation, your certificate will be made available immediately.

If you have received credit for UPN 809-999-08-041-L01-P, you are not eligible for this activity.

Posttest

1. What percent of chronic pain sufferers take a prescription pharmacotherapeutic agent to manage their pain?
a. More than 80%
b. 75%
c. Less than 50%
d. Less than 25%

2. Which of the following is the most appropriate model for understanding the clinical course of pain?
a. The Biomedical Model in Chronic Pain
b. The Biopsychosocial/Neurobehavioral Model
c. The Managed Primary Care Model
d. The Multidisciplinary Biobehavioral Pain Center Model

3. Of the following opioid agonist analgesic therapies, which would have fewer GI side effects and produce fewer withdrawal symptoms than commonly used opioids?
a. Methylnaltrexone
b. Oxycodone IR
c. Tapentadol IR
d. Alvimopan

4. Tapentadol achieves analgesia with the following mechanism(s) of action:
a. Selective serotonin reuptake inhibition
b. μ-Opioid receptor agonism and norepinephrine reuptake inhibition
c. Norepinephrine reuptake inhibition
d. Partial μ-opioid receptor agonism

5. Half of all patients with pain are managed by:
a. Orthopedists
b. Primary care physicians
c. Neurologists
d. Chiropractors

6. One of the primary reasons for ineffective pain management is:
a. Patients are reluctant to discuss pain
b. Physicians feel their education in pain management is poor
c. Pharmacies do not stock the appropriate medications
d. Patients exaggerate their pain

7. Patients being treated with opioids are at risk for developing:
a. Tolerance
b. Physical dependence
c. Addiction
d. All of the above

8. Tolerance is:
a. The result of repeated exposure to a drug that results in decreased effectiveness of the drug
b. An adaptation of the body that requires the maintenance of a specific level of drug in the body
c. A chronic, neurobiologic disease
d. None of the above

9. What is **not** true of physical dependence?
a. Abrupt cessation or rapid dose reduction can result in withdrawal syndromes.
b. A specific level of drug in the body must be maintained.
c. It is a disease with genetic, psychosocial, and environmental factors.
d. Withdrawal syndromes can be avoided by gradually tapering the opioid dose.

10. A treatment plan should:
a. State the objectives of treatment
b. State how treatment will be adjusted to meet the patient's individual needs
c. Require that physicians develop a relationship based on trust
d. All of the above

11. The Drug Enforcement Administration classifies substances in 5 categories (schedule I-V), based on several criteria. Which one is **not** one of those criteria?
a. The substance's potential for abuse
b. Scientific evidence of its pharmacotherapeutic effects
c. Current scientific knowledge of the substance
d. Whether the drug is approved by the US Food and Drug Administration

Posttest Answer Key

1____	2____	3____	4____	5____	6____
7____	8____	9____	10____	11____	

Evaluation Form – 5244 ES 29

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. ***You must complete this evaluation form to receive acknowledgment for completing this activity.***

1. Chronic pain treatment is best accomplished using a biopsychosocial model for disease management.
Strongly Disagree 1 2 3 4 5 6 Strongly Agree

2. A majority of patients with chronic pain require at least 6 months of treatment to get pain under control.
Strongly Disagree 1 2 3 4 5 6 Strongly Agree

3. The "universal precautions" approach has an application in managing risk and results in treating chronic pain.
Strongly Disagree 1 2 3 4 5 6 Strongly Agree

4. Physical dependence on opioids after long-term use is not the same as addiction
Strongly Disagree 1 2 3 4 5 6 Strongly Agree

5. Rates of addiction or abuse resulting from long-term opioid therapy have been estimated to range from 3% to 43%.
Strongly Disagree 1 2 3 4 5 6 Strongly Agree

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree 2 = Disagree 3 = Neutral 4 = Agree 5=Strongly Agree

Extent to Which Program Activities Met the Identified Objectives

After completing this activity, I am now better able to:

- Specify the impact of the undertreatment of pain and inadequate pain relief 1 2 3 4 5
- Identify key issues surrounding the treatment of chronic pain with scheduled and non-scheduled opioid analgesics 1 2 3 4 5
- Outline the risk/benefit ratios of current and future prescription analgesics and formulations 1 2 3 4 5
- Cite the federal regulations regarding prescription pain medications 1 2 3 4 5
- Review national surveillance/monitoring data 1 2 3 4 5
- Identify appropriate roles of the primary care physician and pain specialist in the management of pain patients 1 2 3 4 5

Overall Effectiveness of the Activity

The content presented:

- Was timely and will influence how I practice 1 2 3 4 5
- Enhanced my current knowledge base 1 2 3 4 5
- Addressed my most pressing questions 1 2 3 4 5
- Provided new ideas or information I expect to use 1 2 3 4 5
- Addressed competencies identified by my specialty 1 2 3 4 5
- Avoided commercial bias or influence 1 2 3 4 5

Impact of the Activity

Name one thing you intend to change in your practice as a result of completing this activity:

_____

_____

_____

_____

Please list any topics you would like to see addressed in future educational activities:

_____

_____

_____

_____

Additional comments about this activity:

_____

_____

_____

_____

Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

❒ Yes, I would be interested in participating in a follow-up survey.

❒ No, I'm not interested in participating in a follow-up survey.

If you wish to receive acknowledgment for completing for this activity, please complete the posttest by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876.

Name _____ Degree _____
First Middle Int. Last

Organization _____ Specialty _____

Address _____
Street Address City State Zip Code

E-mail _____

Phone Number ( ) _____ Fax Number ( ) _____

_____
Signature

_____
Date

For Physicians Only

I certify my actual time spent to complete this educational activity to be ____.

❒ I participated in the entire activity and claim 1.25 credits.

❒ I participated in only part of the activity and claim _____ credits.

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Important CME Materials Enclosed

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Time for Change